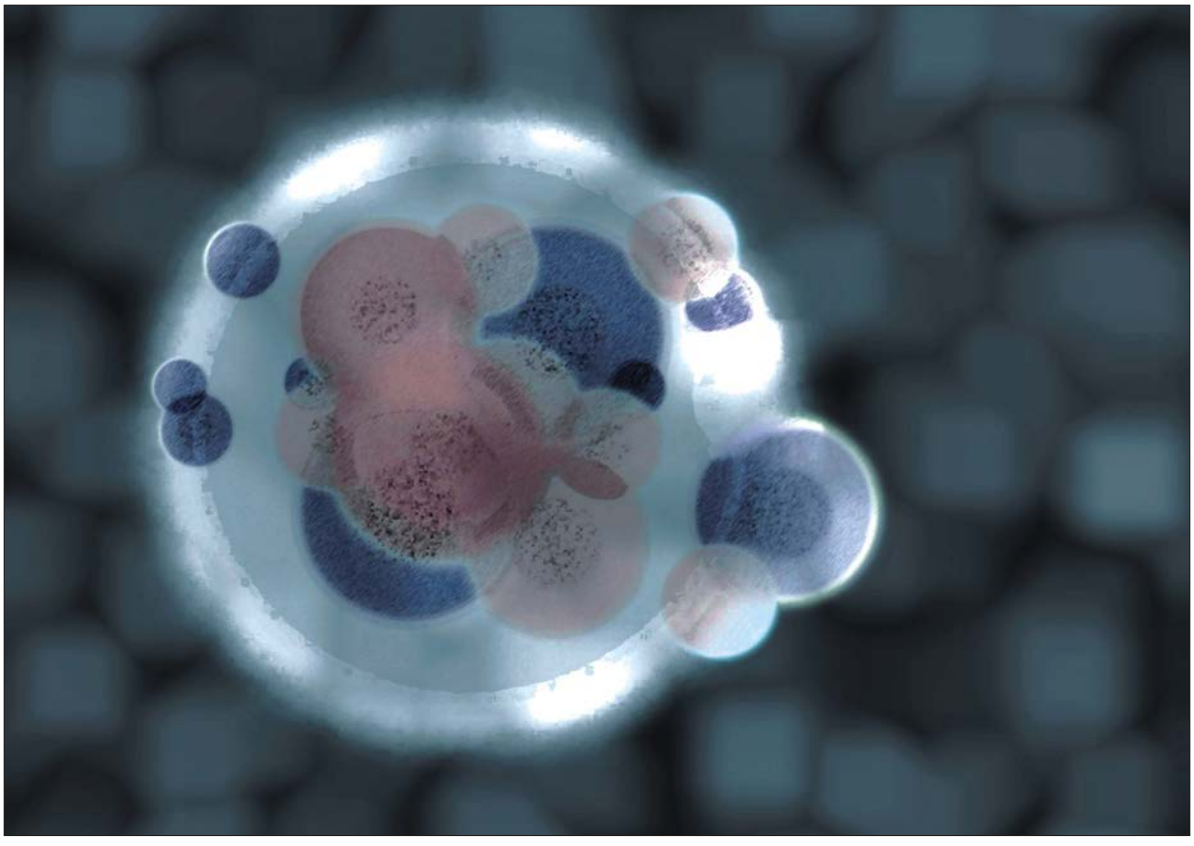

Journal of Biological Sciences

ISSN 1727-3048

science alert

ANSInet
an open access publisher
http://ansinet.com

Journal of Biological Sciences 10 (6): 545-554, 2010
ISSN 1727-3048

Antioxidant System in Adaptation to Intermittent Hypoxia

O. Gonchar and I. Mankovska
Department of Hypoxic States, Bogomoletz Institute of Physiology,
National Academy of Sciences of Ukraine, 4 Bogomoletz St., 01024, Kyiv, Ukraine

Abstract: Intermittent hypoxia (repeated episodes of hypoxia and reoxygenation) (IH) is widespread phenomenon that occurs in a variety of both normal physiologic and pathological conditions. However, the mechanisms underlying IH are not well understood. Numerous studies have shown effectiveness of mild IH in adaptation to hypoxia and in formation of cells resistance to another stresses. It is known that moderate concentration of intracellular ROS is involved in a cascade of intra-cellular redox signaling with subsequent activation of redox-sensitive transcription factors and O_2-responsive genes. Many of the basic events of cell genetic regulation are driven by the oxidant-antioxidant homeostasis, especially by the thiol-disulfide balance. Purpose of the article is to summarize the current information concerning effects of preferentially investigated modes of IH: the chronic intermittent hypobaric hypoxia as well as acute and chronic normobaric short-cycle IH on cells prooxidant/antioxidant balance. We have focused on the regulation of the redox-sensitivity transcription factors such as HIF-1, NF-kB, AP-1 and Nrf2 by oxidants, antioxidants and other factors that influence intracellular redox status and possible participation of these transcription factors in the forming of adaptive responses to hypoxia/reoxygenation.

Key words: Intermittent hypoxia, prooxidant/antioxidant balance, redox equilibrium, transcription factors, adaptation

INTRODUCTION

Both hypoxia (lack of oxygen relative to metabolic needs) and reoxygenation (reintroduction of oxygen to hypoxic tissues) are widespread phenomena because they occur in a variety of normal physiologic conditions (development, physical activity, exposure to hypoxic environment) and are also related to various pathological conditions among which are pulmonary, cardiac and vascular diseases, inflammation, transplantation, cancer, etc.

Repeated episodes of hypoxia and reoxygenation (H/R) Intermittent Hypoxia (IH) have been preferentially investigated in following modes: the Chronic Intermittent Hypobaric Hypoxia (CIHH), the acute and chronic normobaric short-cycle IH (Belaidi *et al*., 2009).

The CIHH is characterized by daily exposure to a sustained (4 to 8 h) period of hypobaric (5000 to 7000 m a.s.l.) hypoxia followed by a return to normoxic conditions. Intermittence is provided by repetition of those stimuli over several days. This model is the most representative for physiological adaptation to high altitude (Ostadal and Kolar, 2007; Dosek *et al.,* 2007).

The short-cycle IH model consists of repetitive brief cycles (i.e., few seconds or minutes) of normobaric hypoxia-normoxia applied daily during various lengths of time. Chronic exposure of brief hypoxic episodes is the main feature of Obstructive Sleep Apnea (OSA), a condition associated with an increased risk of cardiovascular and neurodestructive morbidity (Suzuki *et al*., 2006; Chen *et al*., 2005). At the same time, the short-cycle IH is the basis of Intermittent Hypoxic Training (IHT) that is one of the adaptive training types. The sessions of IHT consist of repeated exposure to 5-15 min hypoxia interrupted by equal periods of recovery and continued several hours daily for a few weeks. It was reported that intermittent hypoxia might effectively stimulate various metabolic processes and this phenomenon is widely used in sports and medicine practice (Tkachouk *et al*., 1994). Investigations performed in our and other laboratories showed that adaptation to intermittent hypoxia could reduce the damage caused by other stresses including ischemia (Cai *et al*., 2003; Park and Suzuki, 2007; Guo *et al*., 2009), intensive physical exercise (Mankovska *et al*., 2009) and more severe and sustained hypoxia (Stroev *et al*., 2005; Gonchar and Mankovskaya, 2009). Clinical and experimental studies have confirmed beneficial effects of IHT on hypoxic ventilatory response, an increase in the red blood cell mass, erythropoietin (Epo) level and aerobic capacity

Corresponding Author: Gonchar Olga, Department of Hypoxic States, Bogomoletz Institute of Physiology NAS of Ukraine, Bogomoletz St., 4, 01024, Kyiv, Ukraine Tel: + 38 044 2562492 Fax: + 38 0442562000

(Clanton and Klawitter, 2001; Vogt *et al*., 2001; Ostadal and Kolar, 2007). These changes in the oxygen transport system are responsible for high resistance to hypoxia, increasing of exercise tolerance and maximal work capacity (Katayama *et al*., 2003; Truijens *et al*., 2003). Long-term IHT is reported to reduce lipid peroxidation (LPO), increase the antioxidant activity and P_{O2} in rat skeletal muscle after exhaustive swimming (Mankovska *et al*., 2009), enhance of mRNA myoglobin, hypoxia-inducible factor-1 (HIF-1) and vascular endothelial growth factor (VEGF) levels in human muscle after acute exercise (Clanton and Klawitter, 2001; Vogt *et al*., 2001). In cardiac muscle, intermittent hypoxic exposure may reduce the risk of coronary heart disease, prevent the onset of arrhythmias and improve myocardial tolerance to chronic hypoxia-induced dysfunction (Guo *et al*., 2009; Park and Suzuki, 2007; Milano *et al*., 2002). The duration, frequency and severity of hypoxic episodes are critical factors determining whether acute or chronic exposure to cyclic IH has beneficial or harmful effects on tissues.

Although, the protective effect of IH has been established, its molecular mechanism, did not receive major attention until recently and thus it remains far from being understood.

The adaptive response is a biological phenomenon, which involves cells reactions at a molecular level to achieve greater cellular resistance against a wide range of physiological stresses, including the Reactive Oxygen Species (ROS) accumulation (Bartosz, 2009). The adaptation mechanism seems to be an organ-specific manner and involves alterations in gene expression and de novo protein synthesis (Sen and Packer, 1996; Semenza, 2009).

More and more evidence is accumulating that a peculiar balance between oxidants and antioxidants is involved in regulation of the intracellular redox state that is a crucial mediator of multiple metabolic, signaling and transcriptional processes in cells (Haddad, 2002). Glutathione and thioredoxine systems as well as protein thiols in the form of cysteine residues are key players in cell redox sensing and regulation (Limon-Pacheco and Gonsebatt, 2009).

Purpose of this study is to summarize the current information about effects of IH on the cell prooxidant-antioxidant homeostasis as well as its involvement in the regulation of adaptive processes through the activation of transcription factors. We have focused on the regulation of gene expression under IH conditions by oxidants, antioxidants and other factors that influence intracellular redox status.

ROS AND INTERMITTENT HYPOXIA

Several studies have reported that exposing cells to hypoxia/reoxygenation increases ROS generation (Li and Jackson, 2002). Under hypoxia, ROS are generated in the cell by several mechanisms including the xanthine-hypoxanthine system, mitochondrial respiratory enzymes, lipoxygenase, certain P-450 enzymes, nitric oxide synthase and membrane-bound NADPH oxidase (Bartosz, 2009; MacFarlane *et al*., 2008; Chandel and Budinger, 2007). It is generally believed that under low oxygen level the two major sites for O_2^- production in the mitochondrial respiratory chain are at complexes I and III (Poyton *et al*., 2009). During hypoxia an accumulation of reducing equivalents within the mitochondrial respiratory sequence can lead to ROS formation by the autooxidation of one or more mitochondrial complexes, such as the ubiquinone-ubiquonol redox couple (MacFarlane *et al*., 2008). Reintroduction of oxygen to the reductive intracellular environment during intermittent reoxygenations could generate the additional amount of ROS that likely was originated from sources other than mitochondria, as for example the xanthine/xanthine oxidase reaction (Li and Jackson, 2002) or NADPH oxidase (Yuan *et al*., 2008; Jun *et al*., 2008).

Both the severity and duration of hypoxia as well as reoxygenation periods may play an important role in the adaptation to IH (Leonard *et al*., 2006; Belaidi *et al*., 2009). Whereas, the excessive ROS production (superoxide and hydroxyl radicals, hydrogen peroxide and after scavenging of O_2^- by nitric oxide, peroxynitrite) has cytotoxic effect and causes LPO, DNA damage, the depletion of intracellular antioxidant defense system, alteration in calcium homeostasis and apoptosis (Li and Jackson, 2002), low levels of ROS may serve as messengers in order to activate adaptive responses through redox-sensitive signaling pathways (Papandreou *et al*., 2005; Bartosz, 2009).

PROOXIDANT-ANTIOXIDANT BALANCE AT DIFFERENT MODELS OF INTERMITTENT HYPOXIA

Biological systems have several defense mechanisms against ROS that may be enzymatic or non-enzymatic in nature. A delicate balance between oxidant and antioxidant components appoints the defense rate of cells from oxidative stress (Bartosz, 2009; Limon-Pacheco and Gonsebatt, 2009). Numerous studies have demonstrated that antioxidant capacity is changed as a result of hypoxia and the ultimate balance between production of free radicals and antioxidative processes at IH directly depends on the experimental hypoxic regimen and

tissue specific resistance to hypoxia/reoxygenation (Gonchar and Rozova, 2007; Jun *et al*., 2008).

Thus, CIHH (6100 m for 3 and 7 days) significantly decreased reduced glutathione (GSH), Glutathione Peroxidase (GP), Glutathione Reductase (GR), superoxide dismutase (SOD) levels in the brain regions and hippocampus was more susceptible to hypoxia (Maiti *et al*., 2006). Later on, Hota *et al*. (2007) confirmed these data and showed that a decrease in GSH level coincident with an increase in glutamate dehydrogenase activity and increase in expression of vesicular glutamate transporter that may lead to impaired cystein uptake, which causes depleted of antioxidant status at hypobaric hypoxia. As suppose some authors, brain, which is rich in polyunsaturated fatty acids and has a high metabolic rate, is a soft target for oxidative damage in hypobaric hypoxia (Maiti *et al*., 2006; Dosek *et al*., 2007). These data were in agreement with study by Singh *et al*. (2001), which was observed a significant decrease in GSH content in muscle as well as GR and Glutathione-S-Transpherase (GST) activities in liver and erythrocytes of hypoxia-exposed rats at 7,620 m (6 h/day for 1, 7, 14 and 21 days), at the same time, in muscle activities of these antioxidant enzymes were increased.

In contrast, the moderate CIHH (380 mm Hg 15 h day^{-1} for 7, 14, 28 days) attenuated iron-induced reductions in GSH content, GSH/GSSG ratio and SOD but had no effect on GP in the substantia nigra of rat brain (Lin *et al*., 2002). It was reported that CIHH (5000 m 6 h day^{-1}, for 28 days) increased activity and protein expression of MnSOD and catalase without affecting the Cu,Zn-SOD and GPx activities in guinea pig myocardial tissue (Guo *et al*., 2009) and this may indicate a critical role of the MnSOD induction in the acquisition of CIHH against I/R injury.

Chronic IH (CIH) with short and severe hypoxic exposures is thought to be a major cause of cardiovascular and neurogenous alterations, which may occur in patients with OSA (Suzuki *et al*., 2006). Prolonged CIH (4-5% O_2 60s+21% O_2 60 sec 8 h day^{-1}, for 5 weeks) that resembles OSA condition results in the increasing sensitiveness of rat heart to ischemia/reperfusion injury and decreases in Cu,Zn-SOD activity (Suzuki *et al*., 2006; Chen *et al*., 2005) as well as in the increasing of mouse brain cortex oxidative damage and decreasing neurocognitive function (Shan *et al*., 2007). Similar findings were demonstrated by Jun *et al*. (2008) that CIH in liver increased the LPO and NADPH oxidase $p47^{phox}$ subunit protein levels but GSH/GSSG was remained and GSH stores were restored after 4 weeks; in contrast, in the cardiovascular system this regime did not affect LPO.

There was observed in our laboratories that moderate IHT (5 cycles of 5 min 12% O_2 and 15 min normoxia, daily for 3 weeks) attenuated basal and stimulated *in vitro* lipid peroxidation as well as O_2^- and H_2O_2 production in both heart, liver cytozol (Gonchar and Mankovska, 2007) and liver, brain mitochondria (Gonchar and Mankovskaya, 2009) of rats exposed to immobilization stress and acute severe hypoxia. Adaptation to moderate H/R enhances in tissues and mitochondria the activity of ROS scavengers such as Mn-SOD, GP and GST. It was demonstrated that the maintenance of GSH-redox cycle by activation of GR and $NADP^+$-dependent isocitrate dehydrogenase in heart and glucose-6-phosphate dehydrogenase in liver cytozol is an integral part of the biochemical adaptive mechanism of oxidative tolerance to new damaging factor. However, these effects do not maintain if in the course of IHT was used severe hypoxic stimulus (7% O_2). It should be noted that more severe regimen of IHT had beneficial effects on mitochondrial antioxidant defense system at its later phase (45 days after cessation of IHT) only (Gonchar, 2008). This is in agreement with the hypothesis of Aa second window of protection of hypoxic preconditioning when oxygen radicals generated during the initial preconditioning period activate the endogenous antioxidant defense at late phase (Chen *et al*., 2003).

Induction of endogenous antioxidants seems is one of the key molecular mechanisms of cell resistance to H/R. Some studies suggest a close correlation between the increase in antioxidant activity and cardioprotection induced by various preconditioning methods. Thus, Park and Suzuki (2007) have indicated that the normalization of infarct size in murine heart after 28 days of IH exposure (2 min 6% O_2 + 2 min 21% O_2 for 8 h day^{-1}) is associated with overexpression of thioredoxin (Trx) protein as well as Trx mRNA levels.

These results are consistent with previous findings showing that the overexpression of antioxidative enzymes can improve the heart contractile function recovery (Guo *et al*., 2009), normalize the infarct size after I/R injury (Park and Suzuki, 2007) and enhance myocardial tolerance to chronic hypoxia-induced dysfunction (Milano *et al*., 2002).

It were demonstrated that preconditioning with repetitive episodes of mild hypoxia essentially modified the reaction to severe hypobaric hypoxia in rat forebrain structures by increasing the expression and activity of Cu,Zn-SOD, Trx -1 and Trx -2 (Stroev *et al*., 2004, 2005).

These data confirm that H/R affects the antioxidant homeostasis, at the same time, antioxidants are actively involved in the formation of cell adaptive responses to the effect of IH.

PARTICIPATION OF ANTIOXIDANTS IN MOLECULAR MECHANISMS OF ADAPTATION TO INTERMITTENT HYPOXIA

Repeated exposures of H/R during IH evolve various O_2^- sensing systems to trigger adaptive mechanisms maintaining cellular and systemic homeostasis (Beguin *et al*., 2007; Belaidi *et al*., 2009). The ROS at IH can act as signal compounds and thereby determine the nature of the hypoxic response (Bartosz, 2009). It is believed that moderate concentration of intracellular ROS is involved in a cascade of intra-cellular redox signaling with subsequent activation of redox-sensitive transcription factors and genes that control the synthesis of protective components (Naduri *et al*., 2008).

Hypoxia-induced gene expression has been implicated in a number of physiological processes, including erythropoiesis, carotid body chemoreceptor function and angiogenesis, all of which enhance the delivery of O_2 to tissue (Wenger, 2002; Chandel and Budinger, 2007). Genes involved in mediating each of these important processes are normally activated by long-term (hours to days) rather than acute (second to minutes) episodes of hypoxia (Ostadal and Kolar, 2007). This is consistent with Cai *et al*. (2003) who showed that IH in contrast to ischemic preconditioning induces protective mechanism by the activation of delayed protection, including the transcriptional regulation by factors such as HIF-1.

Intermittent hypoxia and redox-sensitive transcriptional factors: Studies on cell cultures and animals have shown that IH activates several genes via recruiting specific transcription factors such as HIF, activator protein-1 (AP-1), nuclear factor- kappa B (NF-kB), NF- E2- related factor 2 (Nrf2), nuclear factor of activated T-cells (NFAT) and cAMP-response-element-binding protein (Naduri *et al*., 2008).

Thus, IH up-regulates HIF-1α protein in PC12 cell cultures (Yuan *et al*., 2004, 2008), increases of Epo expression in rat carotid body (Lanı *et al*., 2009). The IH caused activation of NF-kB in cardiovascular tissues (Greenberg *et al*., 2006) and in liver (Savransky *et al*., 2007), increased AP-1 activity and tyrosine hydroxylase mRNA (an AP-1-regulated downstreanı gene) in PC12 cells (Yuan *et al*., 2004), enhanced expression of c-fos in rat brainstem (Greenberg *et al*., 1999). Compared to the same duration and intensity of continuous hypoxia, IH is more potent in activating HIF-1 and c-fos and also results in long-lasting accumulation of HIF-1α and c-fos mRNA (Naduri *et al*., 2008). Acute IH (five cycles of 2 min of 10% O_2 +2 min of 21% O_2) was found to increase an antiapoptopic bcl-x_l and bcl-2 mRNA levels as well as their transcriptional regulator GATA through the promotion of gata-4 gene transcription (Park *et al*., 2007). Deindl *et al*. (2003) have demonstrated that CIHH (5000 m, 4 h day^{-1} for 10 days) increased expression of heme oxygenase-1 (HO-1), transforming growth factor-b1, VEGF, lactate dehydrogenase-A in heart and lung. Expression of c-fos was found up-regulated in the left and right ventricle of heart after 4 h of CIHH. Belaidi *et al*. (2009) have recently confirmed that acute IH activates the iNOS gene and that this is necessary to induce the delayed myocardial preconditioning by acute IH. Beguin *et al*. (2007) have reported that ROS influences on stress-activated kinases and p38 MAPK and ERK1/2 acted as triggers and PKC as a mediator in the acute IH-induced delayed cardioprotection.

Redox-mediated regulation of HIF-1: Cell redox equilibrium influences on an adaptive cross-talk between signaling pathways sensing dynamic variations in pO_2 and genetically regulated transcription factors (Sen and Packer, 1996). Many of the basic events of cell regulation such as protein phosphorylation and binding of transcription factors to consensus DNA sites are driven by the oxidant-antioxidant homeostasis, especially by the thiol-disulfide balance (Haddad, 2002).

Intracellular redox-regulating molecules and enzymes such as GSH, catalase, SOD, GPx, Trx maintain cellular redox status. GSH and GR as well as Trx and thioredoxin reductase exist in all living cells and constitute the major NADPH-dependent protein disulfide redox systems that regulate a large number of transcriptional factors like HIF, NF-kB and AP-1 as well as their regulators (Liu *et al*., 2005).

It is believed that HIF-1 is the main regulator of cellular responses to hypoxia (Wenger, 2002; Chandel and Budinger, 2007). HIF-1 enhances transcription of genes encoding hypoxia-sensitive proteins that promote cellular adaptation and cell survival under conditions of limited oxygen supply (Semenza, 2009). Different mechanisms contribute to HIF-1α induction and include the control of HIF-1α degradation by prolyl hydroxylase (PHD), HIF-1α transactivation by FIH, the degree of HIF-1α synthesis (e.g., translation control), posttranslation modifications of HIF-1α (e.g., phosphorylation) and regulation of the redox state of HIF-1α by Trx1 and redox factor-1 (Ref-1). (Michiels *et al*., 2002; Semenza, 2009). It was reported that overexpression of Trx and Ref-1 significantly potentiated hypoxia-induced HIF-1 DNA binding (Wenger, 2002; Welsh *et al*., 2002; Liu *et al*., 2005).

Antioxidant/prooxidant equilibrium differentially regulates HIF-1α redox sensitivity (Sen and Packer, 1996).

It is considered that SOD can influence on transcriptional factors and genes expression by modulating the cellular redox environment. Kaewpila *et al.* (2008) hypothesize that Mn-SOD affects the expression of redox-sensitive gene, including HIF-1α, by converting O_2^- and have shown that decreasing of Mn-SOD resulted in an increase of HIF-1α protein accumulation under hypoxia. Moderate overexpression of Mn-SOD in MCF-7 cells has been shown to suppress hypoxic accumulation of HIF-1α and VEGF protein at both 1 and 4% O_2 (Wang *et al.*, 2005). Alternatively, overexpressing of Mn-SOD or Cn,Zn-SOD in A549 human lung epithelial cells does not alter HIF-1α stabilization under hypoxic condition, whereas overexpressing of GPx or catalase decreased HIF-1α accumulation at low O_2 levels (Brunelle *et al.*, 2005). In accordance with these data Grzenkowicz-Wydra *et al.* (2004) have shown that overexpression of Cu,Zn-SOD, leading to increased production of H_2O_2, induces HIF-1-dependent mRNA VEGF expression. Zelko and Folz (2005) in cell culture studies have demonstrated that overexpression of EC-SOD decreased hypoxia-induced Epo gene expression and the mechanism for EC-SOD's profound effect is dependent on, at last in part, stabilization of HIF-1α. The disturbance in redox equilibrium by EC-SOD gene knock-out may promote HIF-1α instability and thereby decrease Epo gene expression in the hypoxic kidney (Suliman *et al.*, 2004). Some authors considered that the protective effect of Mn-SOD in H/R is more related to its signaling effect on gene expression rather than its direct antioxidant effect (Pardo and Tirosh, 2009).

The change in the ratio of intracellular GSH/GSSG may also regulate HIF-1 induction during hypoxia. For example, GSSG/GSH increasing can inhibit HIF-1α binding activity (Haddad *et al.,* 2000) and selective inhibition of γ-glutamyl cysteine synthetase (γ-GCS) abrogates hypoxia-induced nuclear localization, stabilization and activation of HIF-1α in developing alveolar epithelium (Haddad and Land, 2000). Moreover, there is substantial evidence supporting the notion that γ-GCS inhibition is accompanied by intracellular accumulation of O_2^- and H_2O_2, believed to play a key role in destabilizing HIF-1α (Haddad *et al.*, 2000). Excessive H_2O_2 inactivates PHD, perhaps by oxidation of active site iron that may contribute to the stabilization of HIF (Michiels *et al.*, 2002; Chandel and Budinger, 2007; Semenza, 2009). In contrast, recent study by Tajima *et al.* (2009) has indicated that the increase in GSSG concentration in HSC-2 cell line may enhance the hypoxic induction of HIF-1α. These discrepancies can be explained by different severity and duration of hypoxic exposures.

Antioxidant- induced activation of the NF-kB and AP-1: NF-kB and AP-1 are implicated in the inducible expression of a wide variety of gene involved in oxidative stress and cellular adaptive response mechanisms. NF-kB first identified as a transcriptional factor that regulates antibody release in B-cells, is central to the regulation and expression of stress response genes in the face of inflammatory and oxidative challenges (Haddad, 2002; Michiels *et al.*, 2002). AP-1 is a heterodimeric complex of proteins (c-Fos and c-Jun) encoded by the proto-oncogenes *c-fos* and *c-jun*. AP-1 activation is associated with cellular growth, differentiation, neuronal excitation and stress responses (Sen and Packer, 1996).

These transcriptional factors are regulated by the intracellular redox state (Michiels *et al.*, 2002). Thus, intracellular Trx and glutathione status influence on AP-1 and NF-kB transactivation (Schenk *et al.*, 1994; Hirota *et al.*, 1997). The oxidation of GSH to GSSG induces the formation of an inactive NF-kB/disulfide complex, thereby inhibiting DNA binding activity (Wenger, 2002; Reynaert *et al.*, 2006). These findings fit well with the previous observation that a decrease in the GSH/GSSG ratio inhibits activation of AP-1 and NF-kB in gastric epithelial cells (Rokutan *et al.*, 1998). Reduced thiols including dithiothreitol, cysteine, dihydrolipoate and Trx enhance the DNA binding of activated NF-kB (Freemerman *et al.*, 1999). Trx is known to enhance the DNA-binding activity of AP-1 (Jun and Fos) by interacting with Ref-1, thereby maintaining the redox status of certain cysteine residues involved in their DNA binding function (Hirota *et al.*, 1997). Redox molecules such as nucleoredoxin, glutaredoxin and Trx have different intracellular localization and differentially regulate of NF-kB and AP-1 activation (Hirota *et al.*, 2000).

Schenk *et al.* (1994) have shown that the Trx regulated the activation of NF-kB and AP-1 in an opposite way. Whereas, NF-kB can be regarded as an oxidative stress-responsive factor that is activated by posttranslation processes, AP-1 has far more complex pattern of regulation and can be activated by prooxidant and antioxidant conditions.

Recent studies suggest interactions between NF-kB and HIF-1. Belaiba *et al.* (2007) reported that NF-kB plays a role in HIF-1α mRNA induction by hypoxia while Rius *et al.* (2008) showed that NF-kB is critical for hypoxia-evoked HIF-1α accumulation as well as HIF-1-mediated transcription in the liver and brain. This observation suggested that a possible cross-talk between HIF-1α and NF-kB is prominent under mild hypoxic conditions.

GSH-associated metabolism is crucial for providing an equilibrium interface between oxidative stress and

adaptive response of cytoprotection. The ROS and RNS may deplete intracellular GSH pools (Li and Jackson, 2002) and that the resulting decrease in GSH/GSSG ratios is accompanied by an increase in intracellular protein mixed disulfides (Limon-Pacheco and Gonsebatt, 2009). Redox-sensitive regulation of c-Jun occurs through S-glutathionylation of Cys-269 as well as through the formation of an inter-molecular disulfide bridge between cysteine residues near the leucine zipper motif (Klatt *et al*., 1999). The AP-1 regulator, Ref-1, also undergoes cysteine oxidation, leading to a loss in c-Fos and c-Jun binding activity (Liu *et al*., 2005). S-glutathionylation of Cys-62 of the p50 subunit prevents binding of the NF-kB transcription factor to cognate sites in gene promoters (Pineda-Molina *et al*., 2001; Michiels *et al*., 2002).

Nrf2 and antioxidant gene expression: Another important mechanism by which cells adapt to oxidative stress involves up regulation of a distinct array of cytoprotective genes responsible for the cells' antioxidant capacity. Some of these genes act to maintain GSH content and activity of antioxidant enzymes. A master regulator of this specific antioxidant phenotype is the transcriptional factor Nrf2 (Jaiswal, 2004; Suzuki *et al*., 2008). Nrf2, similar to NF-kB, plays a significant role in the adaptive response to oxidative stress (Jaiswal, 2004). Nrf2 binds to the Antioxidant Response Element (ARE) sequence, leading to the transcriptional activation of downstream genes encoding GST, aldehyde dehydrogenase, NADPH quinine oxidoreductase, OH-1 and Trx (Kim *et al*., 2001; Bloom *et al*., 2001; Kim *et al*., 2007).

Several studies have indicated a role of Nrf2 in mediating responses to H/R (Leonard *et al*., 2006; Kim *et al*., 2007). An up regulation of Nrf2 and Nrf2-dependent antioxidant gene expression has been demonstrated in ischemic reperfused human liver and renal tissues (Leonard *et al*., 2006). Malec *et al*. (2010) have reported that Trx1, an Nrf2-dependet target gene induces HIF-1α induction under of IH in A549 cells and thus, Trx1 may represent a possible link between Nrf2 and HIF-1α. This suggests that Nrf2 could enhance HIF-1α accumulation by Trx1 in the progressive hypoxic stages of IH.

Nrf2 stability is dependent on cellular redox state (Jaiswal, 2004). This transcription factor is induced in response to oxidative stress, which might be caused by increased levels of endogenously generated ROS (Osburn and Kensler, 2008). Accumulation of ROS in cells may lead to direct Nrf2 activation and its release to the nucleus (Bloom *et al*., 2001). Additional results by Hansen *et al*. (2004) have shown compartment-specific redox control of Nrf2 signaling. Cytoplasmic activation of Nrf2 was regulated by GSH and not by Trx1. In contrast, nuclear expression of an ARE reporter was controlled by nuclear-targeted Trx1 and not by GSH. Similar to Fos, Jun and NF-kB, Nrf2 has a critical Cys-508, which must be in the reduced form to bind to DNA. Oxi dation of Nrf2 blocks its ability to increase gene expression (Hansen *et al*., 2004). As shown with AP-1 and NF-kB, Trx1 reduces Cys-508 in a Nrf2-dependent reaction and restores gene expression (Bloom *et al*., 2001).

Expression levels of Nrf2, nuclear translocation capacity and activation of gene expression were found to be Mn-SOD dependent (Suzuki *et al*., 2008). Pardo and Tirosh (2009) using gene manipulation have shown that Mn-SOD expression has a subsequent influence on Nrf2 expression and expression of its gene – HO-1, Fos, MafK, MafF, Jun.

Although NF-kB, AP-1, Nrf2 and antioxidant enzymes have been implicated in the oxidant tolerance development, the precise relationship between these nuclear transcription factors and endogenous antioxidants under IH has not been defined yet.

CONCLUSIONS

Numerous studies have shown the effectiveness of IHT in adaptation to hypoxia and formation of cells resistance to another stress. It is possible that such cross adaptation (when resistance to one factor induces resistance to other factors) is a polygenic phenomenon that requires the simultaneous activation of multiple stress-responsive genes. The mild oxidative stress during moderate IH could activate O_2-sensing-related transcriptional factors that are associated with adaptive changes in mammalian cell metabolism including the expression of proteins and enzymes that respond to hypoxic stress. These processes promote the induction of own endogenous protective systems.

From the above discussion is clear that the oxidant-antioxidant homeostasis, especially the thiol-disulfide balance has determined cell redox environment and is the critical determinant that regulates activation, stabilization and binding of transcription factors to consensus sites on the DNA.

The transcription factors involved in activating the genes encoding antioxidants during IH have not been unequivocally identified. Most probable candidates include HIF-1, NF-kB, AP-1 and Nrf2, since they can be activated in response to oxidative stress and it is believed that the binding site of these redox- regulated transcription factors are located in the promoter region of several genes encoding antioxidants.

We attempted to summarize what is currently known concerning oxidant/antioxidant-dependent alteration of HIF-1, NF-kB, AP-1 and Nrf2 at hypoxic conditions and possible participation of these transcription factors in the forming of adaptive responses. Unfortunately, IH is much less studied than other forms of hypoxia and the understanding of its protective mechanisms is not determined finally. Deciphering the mechanisms of IH is important not only for our understanding how cells adapt to hypoxia/reoxygenation but also for its potential practical implication in clinic and sports. The explanation of this phenomenon could provide a foundation for development of novel non-pharmacological approaches to a problem of the correction of some oxidative-induced pathological conditions.

REFERENCES

Bartosz, G., 2009. Reactive oxygen species: Destroyers or messengers?. Biochem. Pharmacol., 77: 1303-1315.

Beguin, P., E. Belaidi, D. Godin-Ribuot P. Levy and C. Ribuot, 2007. Intermittent hypoxia-induced delayed cardioprotection is mediated by PKC and triggered by p38 MAP kinase and Erk1/2. J. Mol. Cell Cardiol., 42: 343-351.

Belaiba, R., S. Bonello, C. Zahringer, S. Schmidt, J. Hess, T. Kietzman and A. Gorlach, 2007. Hypoxia up-regulates hypoxia-induceble factor-1 alpha transcription by involving phosphatidylinositol 3-kinase and nuclear factor kappa B in pulmonary artery smooth muscle cells. Mol. Biol. Cell, 18: 4691-4697.

Belaidi, E., A. Ramond, M. Joyeux-Faure, P. Levy, C. Ribuot and D. Godin-Ribuot, 2009. Contrasting Effects of Intermittent Hypoxia on Myocardial Ischemic Tolerance. In: Intermittent Hypoxia: From Molecular Mechanisms to Clinical Application, Hi, L. and T. Serebrovskaya (Eds.). Nova Science Publishers Inc., New York, pp: 3-18.

Bloom, D., S. Dhakshinamoorthy, W. Wang, C. Celli and A. Jaiswal, 2001. Role of NF-E2 Related Factors in Oxidative Stress. In: Cell and Molecular Responses to Stress, Storey, K. and J. Storey (Eds.). Vol. 2. Elsevier, Amsterdam, pp: 229-238.

Brunelle, J., E. Bell, N. Quesada, K. Vercauteren and V. Tiranti *et al*., 2005. Oxygen sensing required mitochondrial ROS but not oxidative phosphorylation. Cell. Metabol., 1: 409-414.

Cai, Z., D. Manalo, G. Wei, E. Rodriguez and K. Fox-Talbot *et al*., 2003. Hearts from rodents exposed to intermittent hypoxia or erythropoietin are protected against ischemia-reperfusion injury. Circ, 108: 79-85.

Chandel, N. and G. Budinger, 2007. The cellular basis for diverse responses to oxygen. Free Radic. Biol. Med., 42: 165-174.

Chen, C., S. Tsai, M. Ma and M. Wu, 2003. Hypoxic preconditioning enhanced renal superoxide dismutase levels in rats. J. Physiol., 552: 561-569.

Chen, L., E. Einbinder, Q. Zhang, J. Hasday, C. Balke and S. Scharf, 2005. Oxidative stress and left ventricular function with chronic intermittent hypoxia in rats. Am. J. Respir. Crit. Care Med., 172: 915-920.

Clanton, T. and P. Klawitter, 2001. Invited Review: Adaptive responses of skeletal muscle to intermittent hypoxia: The known and the unknown. J. Applied Physiol., 90: 2476-2487.

Deindl, E., F. Kolar, E. Neubauer, S. Vogel, W. Schaper and B. Ostadal, 2003. Effect of intermittent hypoxia on gene expression in rat heart and lung. Physiol. Res., 52: 147-157.

Dosek, A., H. Ohno, Z. Acs, A. Taylor and Z. Radak, 2007. High altitude and oxidative stress. Resp. Physiol. Neurobiol., 158: 128-131.

Freemerman, A., A. Gallegos and G. Powis, 1999. NF-kB transactivation is increased but not involved in the proliferative effects of thioredoxin overexpression in MCF-7 breast cancer cells. Cancer Res., 59: 4090-4094.

Gonchar, O. and E. Rozova, 2007. Effects of different modes of interval hypoxic training on morphological characteristics and antioxidant status of heart and lung tissues. Bull. Exp. Biol. Med., 144: 249-252.

Gonchar, O. and I. Mankovska, 2007. Glutathione system adaptation to acute stress in the heart of the rats during different regimes of hypoxia training. Ukr Biokhim Zh., 79: 79-85.

Gonchar, O., 2008. Effect of intermittent hypoxia different regimes on mitochondrial lipid peroxidation and glutathione-redox balance in stressed rats. Cent. Eur. J. Biol., 3: 233-242.

Gonchar, O. and I. Mankovskaya, 2009. Effect of moderate hypoxia/reoxygenetion on mitochondrial adaptation to acute severe hypoxia. Acta Biol. Hung., 60: 185-194.

Greenberg, H., A. Sica, S. Scharf and D. Ruggiero, 1999. Expression of c-fos in the rat brainstem after chronic intermittent hypoxia. Brain Res., 816: 638-645.

Greenberg, H., X. Ye, D. Wilson, A. Htoo, T. Hendersen and S. Liu, 2006. Chronic intermittent hypoxia activates nuclear factor-kappa B in cardiovascular tissues *in vivo*. Biochem. Biophys. Res. Commun., 343: 591-596.

Grzenkowicz-Wydra, J., J. Cisowski, J. Nakonieczna, A. Zarebski and N. Udilova *et al*., 2004. Gene transfer of CuZn superoxide dismutase enhances the synthesis of vascular endothelial growth factor. Mol. Cell Biochem., 264: 169-181.

Guo, H., Z. Zhang, L. Zhang, C. Xiong and C. Feng *et al*., 2009. Chronic intermittent hypoxia protects the heart against ischemia/reperfusion injury through upregulation of antioxidant enzymes in adult guinea pigs. Acta Pharm. Sin., 30: 947-955.

Haddad, J.J. and S.C. Land, 2000. O2-evoked regulation of HIF-1 and NF-kB in perinatal lung epithelium requires glutathione biosynthesis. Am. J. Physiol. Lung Cell. Mol. Physiol., 278: L492-503.

Haddad, J.J., R.E. Olver and S.C. Land, 2000. Antioxidant/prooxidant equilibrium regulates HIF-1 alpha and NF-kappa B redox sensitivity evidence for inhibitionby glutathione oxidation in alveolar epithelial cells. J. Biol. Chem., 275: 21130-21139.

Haddad, J.J., 2002. Antioxidant and prooxidant mechanisms in the regulation of redox(y)-sensitive transcription factors. Cell. Sign., 14: 879-897.

Hansen, J., W. Watson and D. Jones, 2004. Compartmentation of Nrf2 redox control: Regulation of cytoplasmic activation by glutathione and DNA binding by thioredoxin-1. Toxicol. Sci., 82: 308-317.

Hirota, K., M. Matsui, A. Nishiyama K. Mori and J. Yodoi, 1997. AP-1 transcriptional activity is regulated by a direct association between thioredoxin and Ref-1. Proc. Natl. Acad. Sci. USA., 94: 3633-3638.

Hirota, K., M. Matsui, M. Murata, Y. Takashima and F. Cheng *et al*., 2000. Nucleoredoxin, glutaredoxin and thiredoxin differentially regulate NF-kappaB, AP-1 and CREB activation in HEK293 cells. Biochem. Biophys. Res. Commun., 274: 177-182.

Hota, S., K. Barhwal, S. Singh and G. Ilavazhagan, 2007. Differential temporal response of hippocampus, cortex and cerebellum to hypobaric hypoxia: A biochemical approach. Neurochem. Int., 51: 384-390.

Jaiswal, A., 2004. Nrf2 signaling in coordinated activation of antioxidant gene expression. Free Radic. Biol. Med., 36: 1199-1207.

Jun, J., V. Savransky, A. Nanayakkara, S. Bevans, J. Li, P.L. Smith and V.Y. Polotsky, 2008. Intermittent hypoxia has organ-specific effects on oxidative stress. Am. J. Physiol. Regul. Integr. Comp. Physiol., 295: R1274-1281.

Kaewpila, S., S. Venkataraman, G. Buettner and L. Oberley, 2008. Manganase superoxide dismutase modulates Hypoxia-inducible factor 1a induction via superoxide. Cancer Res., 68: 2781-2788.

Katayama, K., H. Matsuo, K. Ishida, S. Mori and M. Miyamura, 2003. Intermittent hypoxia improves endurance performance and sub maximal exercise efficiency. High Alt. Med. Biol., 4: 291-304.

Kim, Y.C., H. Masutani, Y. Yamaguchi, K. Itoh, M. Yamamoto and J. Yodoi, 2001. Hemin-induced activation of the thioredoxin gene by Nrf2: A differential regulation of the antioxidant responsive element by a switch of its binding factors. J. Biol. Chem., 276: 18399-18406.

Kim, Y., J. Ahn, A. Liang, C. Ip, Y. Zhang and Y. Park, 2007. Human prx1 gene is a target of Nrf2 and is up-regulated by hypoxia/reoxygenation: Implication to tumor biology. Cancer Res., 67: 546-554.

Klatt, P., E. Molina, M. De Lacoba, C. Padilla, E. Martinez-Galesteo, J. Barcena and S. Lamas, 1999. Redox regulation of c-Jun DNA binding by reversible S-glutathiolation. FASEB J., 13: 1481-1490.

Lam, S.Y., G. Tipoe and M. Fung, 2009. Upregulation of erythropoietin and its receptor expression in the rat carotid body during chronic and intermittent hypoxia. Adv. Exp. Med. Biol., 648: 207-214.

Leonard, M., N. Kieran, K. Howell, M. Burne and R. Varadarajan *et al*., 2006. Reoxygenation-specific activation of the antioxidant transcription factor Nrf2 mediates cytoprotective gene expression in ischemia-reperfusion injury. FASEB L., 20: E2166-E2176.

Li, C. and R.M. Jackson, 2002. Reactive species mechanisms of cellular hypoxia-reoxygenation injury. Am. J. Physiol. Cell Physiol., 282: C227-C241.

Limon-Pacheco, J. and M. Gonsebatt, 2009. The role of antioxidants and antioxidant-related enzymes in protective responses to environmentally induced oxidative stress. Mutat. Res., 674: 137-147.

Lin, A.M., C.F. Chen and L.T. Ho, 2002. Neuroprotective effect of intermittent hypoxia on iron-induced oxidative injury in rat brain. Exp. Neurol., 176: 328-335.

Liu, H., R. Colvitti, I. Rovira and T. Finkel, 2005. Redox-dependent transcriptional regulation. Circ. Res., 97: 967-974.

MacFarlane, P., J. Wilkerson, M. Lovett-Barr and G. Mitchell, 2008. Reactive oxygen species and respiratory plasticity following intermittent hypoxia. Respir. Physiol. Neurobiol., 164: 263-271.

Maiti, P., S. Singh, A. Sharma, S. Muthuraju, G. Ilavazhagan and P. Banerjee, 2006. Hypobaric hypoxia induces oxidative stress in rat brain. Neurochem. Int., 49: 709-716.

Malec, V., O. Gottschald, S. Li, F. Rose, W. Seeger and J. Hanze, 2010. HIF-1 alpha signaling is augmented during intermittent hypoxia by induction of the Nrf2 pathway in NOX1-expressing adenocarcinoma A549 cells. Free Radic. Biol. Med., 48: 1626-1635.

Mankovska, I., B. Gavenauskas, V. Nosar, O. Gonchar, L. Bratus and N. Kurhalyuk, 2009. Effects of Intermittent Hypoxia on Oxygen-Dependent Processes in Skeletal Muscle Under Endurance Training. In: Intermittent Hypoxia: From Molecular Mechanisms to Clinical Application, Hi, L. and T. Serebrovskaya (Eds.). Nova Science Publishers Inc., New York, pp: 519-533.

Michiels, C., E. Minet, D. Mottet and M. Raes, 2002. Regulation of gene expression by oxygen: NF-kB and HIF-1, two extremes. Free Radic. Biol. Med., 33: 1231-1242.

Milano, G., A.F. Corno, S. Lippa, L.K. von Segesser and M. Samaja, 2002. Chronic and intermittent hypoxia induces different degrees of myocardial tolerance to hypoxia-induced dysfunction. Exp. Biol. Med., 227: 389-397.

Naduri, J., G. Yuan, G. Kumar, G. Semenza and N. Prabhakar, 2008. Transcriptional responses to intermittent hypoxia. Resp. Physiol. Neurobiol., 164: 277-281.

Osburn, W. and T. Kensler, 2008. Nrf2 signaling: An adaptive response pathway for protection against environmental toxic insults. Mutat. Res., 659: 31-39.

Ostadal, B. and F. Kolar, 2007. Cardiac adaptation to chronic high-altitude hypoxia: Beneficial and adverse effects. Resp. Physiol. Neurobiol., 158: 224-236.

Papandreou, I., A. Powell, A. Lim and N. Denko, 2005. Cellular reaction to hypoxia: Sensing and responding to an adverse environment. Mutat. Res., 569: 87-100.

Pardo, M. and O. Tirosh, 2009. Protective signaling effect of manganese superoxide dismutase in hypoxia-reoxygenation of hepatocytes. Free Radic. Res., 43: 1225-1239.

Park, A. and Y. Suzuki, 2007. Effect intermittent hypoxia on oxidative stress-induced myocardial damage in mice. J. Applied Physiol., 102: 1806-1814.

Park, A., N. Nagase, S. Kumar and Y. Suzuki, 2007. Acute intermittent hypoxia activates myocardial cell survival signaling. Am. J. Physiol. Heart Circ. Physiol., 292: H751-H757.

Pineda-Molina, E., P. Klatt, J. Vazquez, A. Marina, M. Garcia de Lacoba, D. Perez-Sala and S. Lamas, 2001. Glutathionylation of the p50 subunit of NF-kappa B: A mechanism for redox-induced inhibition of DNA binding. Biochemistry, 40: 14134-14142.

Poyton, R., K. Ball and P. Castello, 2009. Mitochondrial generation of free radicals and hypoxic signaling. Trends Endocrinol. Metabol., 20: 332-340.

Reynaert, N., A. van der Vliet, A. Guala, T. McGovern and M. Hristova *et al*., 2006. Dynamic redox control of NF-kappaB through glutaredoxin-regulated S-glutathionylation of inhibitory kappaB kinase beta. Proc. Natl. Acad. Sci. USA., 103: 13086-13091.

Rius, J., M. Guma, C. Schachtrup, K. Akassoglou and A. Zinkernagel *et al*., 2008. NF-kappaB links innate immunity to the hypoxic response through transcriptional regulation of HIF-1 alpha. Nature, 453: 807-811.

Rokutan, K., S. Teshima, M. Miyoshi, M. Kawai, T. Nikawa and K. Kishi, 1998. Glutathione depletion inhibits oxidant-induced activation of nuclear factor-kappaB, AP-1 and c-Jun/ATF-2 in cultured guinea-pig gastric epithelial cells. J. Gastroenterol., 33: 646-655.

Savransky, V., A. Nanayakkara, A. Vivero, J. Li and S. Bevans *et al*., 2007. Chronic intermittent hypoxia predisposes to liver injury. Hepatology, 45: 1007-1013.

Schenk, H., M. Klein, W. Erdbrugger, W. Droge and K. Schulze-Osthoff, 1994. Distinct effects of thioredoxin and antioxidants on the activation of transcription factors NF-kB and AP-1. Proc. Natl. Acad. Sci. USA., 91: 1672-1676.

Semenza, G., 2009. Regulation of Oxygen homeostasis by Hypoxia-Inducible Factor 1. Physiology, 24: 97-106.

Sen, C.K. and L. Packer, 1996. Antioxidant and redox regulation of gene transcription. FASEB J., 10: 709-720.

Shan, X., L. Chi, Y. Ke, C. Luo, S. Qian, D. Gozal and R. Liu, 2007. Manganese superoxide dismutase protects mouse cortical neurons from chronic intermittent hypoxia-mediated oxidative damage. Neurobiol. Dis., 28: 206-215.

Singh, S., P. Vats, M. Kumria, S. Ranganathan, R. Shyam, M. Arora, C. Jain and K. Sridharan, 2001. Effect of high altitude (7,620m) exposure on glutathione and related metabolism in rats. Eur. J. Applied Physiol., 84: 233-237.

Stroev, S., T. Gluschenko, E. Tjulkova, E. Rybnikova, M. Samoilov and M. Pelto-Huikko, 2005. The effect of preconditioning on the Cu,Zn superoxide dismutase expression and enzyme activity in rat brain at the early period after severe hypobaric hypoxia. Neurosci. Res., 53: 39-47.

Stroev, S., T. Gluschenko, E. Tjulkova, G. Spyrou and E. Rybnikova *et al*., 2004. Preconditioning enhanced the expression of mitochondrial antioxidant thioredoxin-2 in the forebrain of rats exposed to severe hypobaric hypoxia. J. Neurosci. Res., 78: 563-569.

Suliman, H., M. Ali and C. Piantadosi, 2004. Superoxide dismutase-3 promotes full expression of the EPO response to hypoxia. Blood, 104: 43-50.

Suzuki, Y., V. Jain, A. Park and R. Day, 2006. Oxidative stress and oxidant signaling in obstructive sleep apnea and associated cardiovascular diseases. Free Radic. Biol. Med., 40: 1683-1692.

Suzuki, T., V. Kelly, H. Motohashi, O. Nakajima, S. Takahkshi, S. Nishimura and M. Yamamoto, 2008. Deletion of the selenocysteine tRNA gene in macrophages and liver results in compensatory gene induction of cytoprotective enzymes by Nrf2. J. Biol. Chem., 283: 2021-2030.

Tajima, M., Y. Kurashima, K. Sugiyama, T. Ogura and H. Sakagkmi, 2009. The redox state of glutathione regulates the hypoxic induction of HIF-1. Eur. J. Pharm., 606: 45-49.

Tkachouk, E., A. Gorbachenkov, A. Kolchinskaya and I. Ehrenburg, 1994. Adaptation to Interval Hypoxia for Prophylaxis and Therapy. Hypoxia Med. Ltd., Moscow, Russia.

Truijens, M.J., H.M. Toussaint, J. Dow and B.D. Levine, 2003. Effect of high-intensity hypoxic training on sea-level swimming performances. J. Applied Physiol., 94: 733-743.

Vogt, M., A. Puntschart, J. Geiser, C. Zuleger, R. Billeter and H. Hoppeler, 2001. Molecular adaptations in human skeletal muscle to endurance training under simulated hypoxic conditions. J. Applied Physiol., 91: 173-182.

Wang, M., J.S. Kirk, S. Venkataraman, F.E. Domann and H.J. Zhang *et al*., 2005. Manganase superoxide dismutase suppresses hypoxic induction of Hypoxia-inducible factor 1a and vascular endothelial growth factor. Oncogene, 24: 8154-8166.

Welsh, S.J., W.T. Bellamy, M.M. Briehl and G. Powis, 2002. The redox protein thioredoxin-1 (Trx-1) increases hypoxia-inducible factor 1 alpha protein expression: Trx-1 overexperssion results in increased vascular endothelial growth factor production and enhanced turmor angiogenesis. Cancer Res., 62: 5089-5095.

Wenger, R.H., 2002. Cellular adaptation to hypoxia: O_2-sensing protein hydroxylases, hypoxia-inducible transcription factors and O_2-regulated gene expression. FASEB J., 16: 1151-1162.

Yuan, G., G. Adhikary, A. McCormick, J. Holcroft, G. Kumar and N. Prabhakar, 2004. Role of oxidative stress in intermittent hypoxia-induced immediate early gene activation in rat PC12 cells. J. Physiol., 557: 773-783.

Yuan, G., J. Naduri, S. Khan, G. Semenza and N. Prabhakar, 2008. Induction of HIF-1a expression by intermittent hypoxia: Involvement of NADPH oxidase, Ca2+ signaling, prolyl hydroxylases and mTOR. J. Cell Physiol., 217: 674-685.

Zelko, I. and R. Folz, 2005. Extracellular superoxide dismutase functions as a major repressor of hypoxia-induced erythropoietin gene expression. Endocrinology, 146: 332-340.