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Intermittent Hypoxia Research in the Former Soviet Union and the Commonwealth of Independent States: History and Review of the Concept and Selected Applications

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ABSTRACT

Serebrovskaya, Tatiana V. Intermittent hypoxia research in the former Soviet Union and the Commonwealth of Independent States: History and review of the concept and selected applications. *High Alt Med Biol* 3:205–221, 2002.—This review aims to summarize the basic research in the field of intermittent hypoxia in the Soviet Union and the Commonwealth of Independent States (CIS) that scientists in other Western countries may not be familiar with, since Soviet scientists were essentially cut off from the global scientific community for about 60 years. In the 1930s the concept of repeated hypoxic training was developed and the following induction methods were utilized: repeated stays at high-mountain camps for several weeks, regular high altitude flights by plane, training in altitude chambers, and training by inhalation of low-oxygen-gas mixtures. To the present day, intermittent hypoxic training (IHT) has been used extensively for altitude preacclimatization; for the treatment of a variety of clinical disorders, including chronic lung diseases, bronchial asthma, hypertension, diabetes mellitus, Parkinson's disease, emotional disorders, and radiation toxicity, in prophylaxis of certain occupational diseases; and in sports. The basic mechanisms underlying the beneficial effects of IHT are mainly in three areas: regulation of respiration, free-radical production, and mitochondrial respiration. It was found that IHT induces increased ventilatory sensitivity to hypoxia, as well as other hypoxia-related physiological changes, such as increased hematopoiesis, alveolar ventilation and lung diffusion capacity, and alterations in the autonomic nervous system. Due to IHT, antioxidant defense mechanisms are stimulated, cellular membranes become more stable, Ca^{2+} elimination from the cytoplasm is increased, and O_2 transport in tissues is improved. IHT induces changes within mitochondria, involving NAD-dependent metabolism, that increase the efficiency of oxygen utilization in ATP production. These effects are mediated partly by NO-dependent reactions. The marked individual variability both in animals and humans in the response to, and tolerance of, hypoxia is described. Studies from the Soviet Union and the CIS significantly contributed to the understanding of intermittent hypoxia and its possible beneficial effects and should stimulate further research in this direction in other countries.

Key Words: hypoxic ventilatory response; catecholamines; mitochondrial respiration; nitric oxide; free radicals; antioxidant enzymes

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INTRODUCTION

In children and adults, profound, prolonged hypoxia may cause disability and even death. Less clear are the effects of tolerable, brief hypoxia for a few minutes or of transient hypoxia lasting one to several hours. Particularly at issue are the effects in humans of such transient bouts of hypoxia when repeated many times, a practice designated as intermittent hypoxia. Furthermore, when intermittent hypoxia as a specific protocol is employed to accomplish a particular aim, for example, acclimatization to high altitude, we use the term *intermittent hypoxic training* or IHT. While interest in intermittent hypoxia has increased only over the last 5 years in Western Europe and North America, there has been intense interest in this field in the former Soviet Union and CIS (Commonwealth of Independent States) for many decades. However, because many of the scientific publications were in Russian or Ukrainian and because they were not widely available in other countries, these research findings remained relatively unknown. This review aims to summarize some of those studies that scientists in Western countries may not be familiar with. Because of the substantial body of literature in this area and the limited scope of this review, we will focus here on the respiratory effects of intermittent hypoxia in healthy humans and animals and on some possible mechanisms of these effects. The interested reader is referred to more extensive recent scientific and historical reviews and investigative reports in Russian and Ukrainian, particularly as related to the potential therapeutic effects of intermittent hypoxia (Berezovsky et al., 1985; Karash et al., 1988; Meerson et al., 1989; Anokhin et al., 1992; Berezovskii and Levashov, 1992; Donenko, 1992; Ehrenburg, 1992; Fesenko and Lisyana, 1992; Vinnitskaya et al., 1992; Serebrovskaya et al., 1998a,b; Volobuev, 1998; Chizhov and Bludov, 2000; Ragozin et al., 2000). Noted also is the use of IHT in the prophylaxis of professional occupational diseases (Berezovsky et al., 1985; Karash et al., 1988; Serebrovskaia et al., 1996) and in sports (Volkov et al., 1992; Radzievskii, 1997; Kolchinskaya et al., 1998, 1999). Recent reviews from Western Europe and North America are also given (Bavis et al., 2001; Clanton and Klawitter, 2001; Fletcher, 2001; Gozal and Gozal, 2001; Mitchell et al., 2001; Neubauer, 2001; Prabhakar, 2001; Prabhakar et al., 2001; Wilber, 2001).

As indicated in the following section, Soviet scientists were working in isolation for decades, and acceptance of their ideas and findings will require confirmation by others, and, indeed, confirmation and even reconfirmation is fundamental in science. Because of this and because of the substantial amount of work done in the CIS and other countries, a critical evaluation of its scientific validity is beyond the scope of this report, which instead aims at exposition of the work done by CIS scientists.

HISTORICAL ASPECTS

Background

A historical evaluation of scientific achievements is a thankless job, because of the danger of omitting the research of men and women who have brought appreciable advancement to particular scientific problems. Nevertheless, using large brush strokes, I will attempt to paint the basic picture of intermittent hypoxia as developed in the former Soviet Union. First, to put Soviet science into perspective, it is important to consider that Russian and Ukrainian scientists were essentially cut off from the global scientific community for six decades, as though they were cloistered in a carefully controlled greenhouse. Especially during the Stalin era, excessive politicization led to vulgarization of scientific ideas with official pronouncement of pseudoscientific "discoveries" (O. Lepeshinska, T. Lysenko, etc.; see Mirsky, 1990), administrative dicta, and frank persecution. Furthermore, outstanding scientists such as academicians L. Orbeli, V. Parin, E. Kreps, P. Anohin, A. Speransky, and L. Shtern were sentenced to prison or prison camps by judges who were political figures without any scientific background (Kreps, 1989). If a publication failed to mention the name of Stalin, there were serious consequences for the scientist. It was as though Soviet science was opposed to science from other countries. The natural results of an arbitrary and totalitarian rule were broken

communications, isolation, and eradication of free thought. For example, in 1948 a special session of an Academy of Biological Sciences denounced genetics as bourgeois pseudoscience, and geneticists were demoted and arrested. The development of all biological science in the Soviet Union was retarded for many years.

Some early Soviet pioneers

But, despite this dreadful situation, scientists continued to work. In the field of hypo-, and hyperbaria, the Soviet Barometric Laboratory was founded the 1930s in the Leningrad Military–Medical Academy. From 1946 to 1949, O. Gazenko, V. Zvorikin, and others conducted detailed studies of the effects of a wide range of hypoxic challenges, including convulsions, on the central nervous system. A. Panin, O. Sydorov, V. Skripin examined relationships between acapnia and hypoxia at high altitude. In the area of hyperbaria, P. Gramenytsky, A. Brestkin, and L. Orbeli began substituting helium for nitrogen in the inspired air (see the reviews by Sergeev, 1962, and Brestkin et al., 1984). Based on these and the investigations by A. Lebedinsky, V. Parin, and O. Gazenko, the fundamental principles for artificial atmospheres in space vehicles were worked out, ushering in the new era of space biology and medicine and leading to the space flight of the first cosmonaut, Juri Gagarin.

Intermittent hypoxia in altitude chambers

The concept of repeated hypoxic training arose before World War II because of the need for altitude acclimatization of Soviet pilots, who flew in open cockpits to altitudes of 5000 to 6000 m (16,000 to 19,700 ft) (Streltsov, 1939). In 1934, N. N. Sirotinin conducted the first research in the field (see the review by Ivashkevich and Serebrovskaya, 2000), seeking effective methods for preacclimatization. Although Sirotinin did not perform experiments using intermittent hypoxia, he proposed that only a few days at altitude would increase tolerance to subsequent hypoxic exposure (Sirotinin, 1940, 1963). From such studies the concept emerged that intermittent, repeated exposures to altitude could induce acclimatization. In the 1930s, methods to increase the endurance to high altitude flights included a stay at high altitude camps for several weeks, regular high-altitude flights by airplane, training in altitude chambers, and inhalation of low-oxygen mixtures (Gurvich, 1938; Krotkov, 1939). Numerous studies showing the efficacy of repeated decompressions in a chamber were carried out at that time (Appolonov, Mirolyubov, Egorov, Ctreltsov, and Kudrin; see Rozenblyum, 1943). As was usual, subjects were exposed to 5000 m for 1 h/d, over several days, for a total of 7 to 11 exposures. During successive altitude exposures, compared with the initial exposure, the higher ventilation and blood arterial oxygen saturation, together with the lower blood P_{CO_2}, implied that ventilatory sensitivity to hypoxia had been increased. Furthermore, the residua of these effects were detected for up to 4 weeks. Fainberg and Osypov (see Gurvich and Fainberg, 1938) reported that 30-min to 3-h exposures every 2 to 3 d, for a total of nine exposures, increased the concentration of hemoglobin by up to 12% and red blood cells by up to 22%. Soviet studies such as these led to altitude training of paratroopers and jumps by a man, Kaitanov, and two women, Pyasetskaya and Shishmariova, from record altitudes. Later, in 1970s, Agadzhanyan and Mirrakhimov (1970), Katkov et al. (1979), Kovalenko et al. (1981), and others showed that a gradual adaptation to hypobaric hypoxia not only facilitated acclimatization, but also improved the working capacity and endurance of athletes and spacemen (see also the reviews by Gippenreiter and West, 1996; Grigorjev and Fedorov, 1998).

Intermittent hypoxia using inhaled gas

Because transport of pilots to mountain environments or utilization of chambers proved expensive and inconvenient, as early as 1938 N. Golubov, R. Levy, and L. Shik (see Vorontsov et al., 1959) utilized inhalations of hypoxic gas mixtures for training pilots. Egorov and Alexandrov on the basis of Paul Bert's method of rebreathing with CO_2 absorption, created their own equipment, a device named EA-4, adding oxygen to maintain the O_2 level constant (see Gurvich and Fainberg, 1938). In the intervening years to the present, intermittent hypoxia has been used extensively in the So-

viet Union and the CIS not only for altitude preacclimatization (Gorbachenkov et al., 1994), but also it has been proposed for treatment of a variety of clinical disorders, including chronic lung diseases and bronchial asthma in children and adults (Meerson et al., 1989; Anokhin et al., 1992; Berezovskii and Levashov, 1992; Donenko, 1992; Ehrenburg and Kordykinskaya, 1992; Fesenko and Lisyana, 1992; Redzhebova and Chizhov, 1992; Vinnitskaya et al., 1992; Lysenko et al., 1998; Serebrovskaya et al., 1998b; Chizhov and Bludov, 2000; Ragozin et al., 2000, 2001), hypertension (Meerson et al., 1989; Potievskaya and Chizhov, 1992; Rezapov, 1992), emotional disorders (Gurevich et al., 1941), diabetes mellitus (Kolesnyk et al., 1999; Zakusilo et al., 2001), Parkinson's disease (Kolesnikova and Serebrovskaya, 1998; Serebrovskaya et al., 1998a), inflammatory processes (Tkatchouk, 1994; Tsvetkova and Tkatchouk, 1999), radiation toxicity (Karash et al., 1988; Sutkovyi et al., 1995; Serebrovskaia et al., 1996; Strelkov, 1997; Strelkov and Chizhov, 1998), and certain occupational diseases (Berezovsky et al., 1985; Karash et al., 1988; Rushkevich and Lepko, 2001). Consideration of all these is beyond the scope of this review. IHT has become so popular in the CIS that special devices have been developed for its administration (Nemerovskii, 1992), including a hermetically sealed chamber for up to seven people (Berezovskii and Levashov, 2000a), and open circuit (Tsvetkova and Tkatchouk, 1999; Berezovskii and Levashov, 2000b) or rebreathing with CO_2 control (Serebrovskaya et al., 1999a) for individuals. Polymer membranes, which can separate O_2 and N_2, are convenient for generating the hypoxic gas mixtures in open circuit devices and chambers (Rozhanchuk et al., 1992; Berestyuk et al., 2001).

INTERMITTENT HYPOXIC TRAINING AND VENTILATION

Intermittent hypoxia, repeatedly administered using one of numerous protocols, has been termed intermittent hypoxic training (IHT). Because the use of intermittent hypoxia appears to imitate some aspects of altitude acclimatization, a question was whether a program of IHT would enhance respiratory sensitivity to hypoxia, a key element in acclimatization. If IHT enhanced the ventilatory response to acute hypoxia, this would support the concept that there was upregulation of the ventilatory response to hypoxia, involving sensitivity of the carotid body or the activities of its afferent nerves. The strategy, then, was to examine the hypoxic ventilatory response in healthy men before and after the administration of IHT. In eighteen 23-year-old healthy men, IHT consisted of daily isocapnic, hypoxic exposures for 14 days (Serebrovskaya et al., 1999a). Each daily session lasted about 30 min and consisted of three 6-min bouts of hypoxia (with intervening normoxia), where the minimal end tidal P_{O_2} values ranged from about 50 mmHg during the first few daily sessions down to 35 mmHg during the final days of the study. Compared to the pretraining measurements, the hypoxic ventilatory responses after the 2 weeks of training were enhanced, as shown in Fig. 1. For the entire cohort, the ventilation at a hypoxic $P_{ET_{O_2}}$ of 45 mmHg increased from 30.4 + 1.9 to 43.6 + 4.2 L/min, an increase of nearly 50%. In pre- versus post-IHT, the end tidal $P_{ET_{O_2}}$ was unchanged, 37.6 versus 38.1 mm Hg, suggesting that ventilation during normoxia was not affected by IHT. Other studies confirmed that IHT did not alter the hypercapnic ventilatory response, suggesting that the effects are selective for the hypoxic response (Serebrovskaya and Ivashkevich, 1992; Kolesnikova and Serebrovskaya, 2001).

In the above study, although each subject acted as his own control, there was no sham control group. Thus it could not be ruled out that the ventilatory manipulation itself could have produced the results. Therefore, the effects of IHT were subsequently examined in other groups of subjects (Serebrovskaya et al., 1999b; Bernardi et al., 2001). For example, in the investigation of Bernardi et al. (2001), of the 18 young healthy men from the Ukrainian Army, 12 were randomly assigned to the test group and had 14 consecutive days of IHT consisting of 1-h daily sessions, with four bouts of isocapnic hypoxia ($P_{ET_{O_2}}$ values down to 35 to 40 mmHg), each bout lasting 5 to 7 min. The six control subjects had a sham procedure, with the same sequence of events, but without hy-

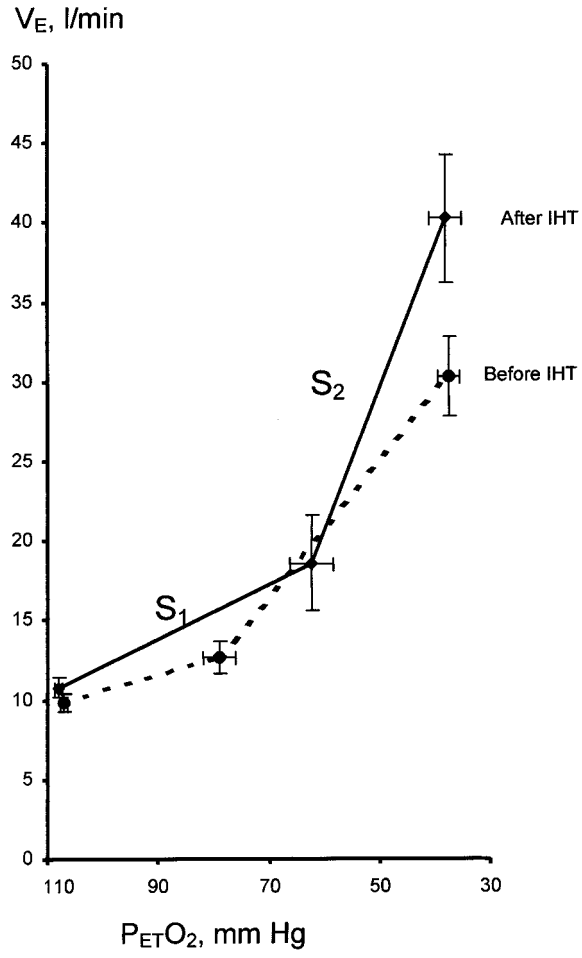

FIG. 1. Ventilatory responses to isocapnic progressive hypoxia in healthy young males before and after intermittent hypoxic training. V_E: expired minute ventilation; $P_{ET}O_2$: end-tidal P_{O_2}; S_1 and S_2: slopes of mild and sharp increase in ventilation, respectively. Eighteen healthy male subjects (mean 22.8 ± 2.1 yr) participated in the study. $P_{ET}CO_2$ was maintained at the initial pretest concentration for each subject, typically 38 to 40 mmHg, throughout the training period.

poxia. Compared to the pretraining measurements, the hypoxic ventilatory responses after the 2 weeks of hypoxic training were enhanced, as determined by the shape factor 'A' (Weil et al., 1970), which increases with increasing hypoxic ventilatory response. 'A' increased from 268 ± 59 to 984 ± 196 in the test group ($p = 0.003$) and did not change significantly in the control group (from 525 ± 180 to 808 ± 245, $p > 0.1$). In both studies, 2 weeks of IHT increased the hypoxic ventilatory response, which was taken to indicate an increased hypoxic responsiveness of the carotid body with altitude acclimatization. Examination of the time course has suggested that the enhancement of ventilatory sensitivity begins with the first hypoxic exposure, and approaches a plateau by the third day (Serebrovskaya, 1992; Serebrovskaya and Ivashkevich, 1992). If so, then in normal humans only a few minutes of daily hypoxic exposure rapidly induces detectable increments in hypoxic ventilatory response, a hallmark of altitude acclimatization.

However, the effects of altitude acclimatization and IHT differ. Hypocapnia occurs with altitude acclimatization and ventilation remains increased for days after the subjects return to sea level. By contrast, in the two above studies, eucapnia was maintained during the hypoxic exposures and neither normoxic ventilation nor normoxic P_{CO_2} was altered by IHT, suggesting that only the hypoxemia and not changes in P_{CO_2} (or pH) were involved. The importance of hypoxia alone has been emphasized by Bisgard in his studies in instrumented, awake goats, a species with very rapid ventilatory acclimatization to hypoxia (see the review; Bisgard, 1994). When isolated carotid bodies were exposed to eucapnic hypoxia, ventilatory acclimatization occurred, but, by contrast, there was little or no ventilatory acclimatization when the carotid bodies were normoxic, while the rest of the body and/or the brain alone were made hypoxic. Changing CO_2, either for the carotid body or the brain, did not induce ventilatory acclimatization to hypoxia. The work from Bisgard's laboratory suggested that ventilatory acclimatization to hypoxia in the goat depends almost exclusively on the carotid body's response to low oxygen. If similar mechanisms operate in humans, then ventilatory acclimatization to hypoxia, operating via the carotid body and independent of changes in pH or P_{CO_2}, can be induced by IHT. What is remarkable is that such brief periods of hypoxia can have such clearly measurable increases in the ventilatory response to hypoxia.

In addition to increasing hypoxic ventilatory sensitivity, CIS investigators have reported that IHT increases tidal volume and alveolar blood flow during exercise, improves matching of ventilation to perfusion, increases lung diffusion capacity, redistributes peripheral blood flow during exercise, decreases

heart rate, increases stroke volume, and increases blood erythrocyte counts (Volkov et al., 1992; Kolchinskaya, 1993; Radzievskii, 1997; Kolchinskaya et al., 1999; Maluta and Levashov, 2001). These effects have been considered to be beneficial in training athletes (Volkov et al., 1992; Radzievskii, 1997). Such findings await independent confirmation from others.

INTERMITTENT HYPOXIC TRAINING AND THE AUTONOMIC NERVOUS SYSTEM

From 1938 to 1943, pilots repeatedly exposed to hypoxia in altitude chambers showed decreases in heart rate and arterial pressure on subsequent hypoxic exposure (Gurvich, 1938; Krotkov, 1939; Miroljubov, 1939; Streltsov, 1939; Alperin and Berger, 1943; Rozenblyum, 1943), suggesting that the autonomic system had been affected by this training procedure. Then, in 1947, Gazenko and Kuznetsov, using men and animals, investigated the sympathetic response to intermittent hypoxia, which led to a recommendation for its use in pilots performing altitude flights (O.G. Gazenko and A.P. Apollonov, in 1950). Nikolai Sirotinin, in 1948 and 1957, considered the autonomic nervous system changes with hypoxia, including intermittent hypoxia, as primary factors in adaptation and concluded (1967), "Between sympathetic and parasympathetic systems there exists not antagonism but synergism." Later, Meerson (1978) found that exposure of rats to 5000 m 4 h/d for 30 d decreased systemic arteriolar tone and inhibited development of an inherited form of hypertension.

In part, these early findings led us to investigate IHT effects on the dopaminergic system. Healthy persons with low blood levels of dopamine and its precursor, dihydroxyphenylalanine, were found to have relatively large ventilatory responses to acute hypoxia (Serebrovskaya et al., 1996; Kolesnikova et al., 1999). In addition, and to follow up on the earlier work, particularly the concepts of Sirotinin, we performed studies to examine more specifically how IHT affected the autonomic nervous system in normal persons. We utilized the noninvasive spectral analysis of heart rate to assess the relative contributions of the sympathetic and parasympathetic systems (Bernardi et al., 2001). During normoxia there were no measurable autonomic changes either in the group receiving the hypoxic training nor in the control group. However, after IHT the increase in heart rate during the hypoxic exposure was nearly abolished, whereas in the control group the sham "training" in no way prevented the increase in rate during acute hypoxia. The spectral analysis suggested that after IHT there was greater parasympathetic preponderance during the hypoxic challenge than in the control group. These novel studies conducted in Ukraine suggested that IHT mimicked the usual acclimatization to high altitude, with its primarily greater parasympathetic activity (Reeves, 1993; Hughson et al., 1994). Such activation of the parasympathetic system by IHT was supported by experiments in rats (Doliba et al., 1993; Kurhalyuk et al., 2001a,b, see below).

TISSUE MECHANISMS WITH INTERMITTENT HYPOXIA

As summarized above, research in the Soviet Union and the CIS over several decades has indicated remarkable, even surprising, effects of intermittent hypoxia. Among these effects are that brief hypoxic stimuli of only several minutes per day for only a few days give responses that last many days, even weeks, and also that IHT apparently affects a multitude of normal functions and disease states. Probably, the evolution of tissue mechanisms relative to IHT originated in the 1970s and 1980s from Soviet studies of acute hypoxia (Kondrashova et al., 1973; Lukyanova et al., 1982; Lukyanova and Korablev, 1982; Lukyanova, 1989). This work, as well as more recent studies (Lukyanova, 1997; Sazontova et al., 1997; Kondrashova et al., 1997; Temnov et al., 1997; Lebkova et al., 1999), indicated that the basic molecular response to any type of hypoxic challenge involves the mitochondrial enzyme complexes (MchEC). There is evidence that energy metabolism under acute hypoxia is affected even before a significant decrease in oxygen con-

sumption becomes measurable and before cytochrome c oxidase (CO) activity is significantly reduced. In the cascade of hypoxia-induced metabolic alterations, MchEC I is most sensitive to intracellular oxygen shortage. The reversible inhibition of MchEC I leads to both the suppression of reduced equivalent flux through the NAD-dependent site of the respiratory chain and the emergency activation of compensatory metabolic pathways, primarily the succinate oxidase pathway. The switch of energy metabolism to this pathway is the most efficient energy-producing pathway available in response to a lack of O_2 (Lukyanova et al., 1982). Intensification of hypoxia leads to propagation of the pathological process toward the cytochromes in the respiratory chain. Electron transport in the region of the b–c cytochromes becomes inactivated first. Only in the near absence of oxygen (anoxia) is CO inhibited.

Skulachev (1996) proposed a two-stage mechanism that allows mitochondria to regulate O_2 concentrations and to protect against oxidative stress: (1) "soft" decoupling of oxidative phosphorylation for "fine-tuning" and (2) decrease of the reduction level of respiratory chain components by opening nonspecific mitochondrial inner membrane pores as a mechanism to cope with massive O_2 excess. As Skulachev (1995) discussed, it is well established that oxygen has a very high affinity to cytochrome oxidase and other oxidases of the respiratory chain with Michaelis–Menten constants (K_m) less than $1 \cdot 10^{-6}$ mol/L. However, parallel nonenzymatic processes result in $O_2^{\cdot -}$ formation. This is especially the case when O_2 concentrations reach the capacity of the respiratory chain enzymes. Reduction in O_2 concentrations leads to an exponential decrease in radical formation. Skulachev (1995) hypothesizes that mitochondria have a mechanism for "soft" decoupling in stage 4 of the respiratory chain. This mechanism prevents the complete inhibition of respiration, the complete reduction of respiratory carriers, and the accumulation of reactive compounds such as ubisemiquinone ($CoQ^{\cdot -}$). Such a mechanism will be activated, for example, if the capacity of the respiratory chain is decreased due to a reduced availability of ADP. In contrast to the constriction of capillaries, which prevents undesirably high O_2 concentrations in tissue, "soft" decoupling allows fine-regulation on an intracellular level. When this system turns out to be insufficient, a less selective mechanism with a higher capacity is activated. According to Skulachev's hypothesis, such a mechanism may be based on the activation of pores in the mitochondrial membrane. These pores are permeable for intramitochondrial compounds with a molecular weight of less than 1.5 kDa and are cyclosporine sensitive. Because of the large diameter of these pores, opening results in immediate equilibration of all membrane gradients, including H^+ and respiratory substrates. As a result, $\Delta\mu_{H^+}$ is completely dissipated. Respiration reaches maximal rates and is only limited by the activity of respiratory enzymes, thus reducing O_2 concentrations at a high rate without energy accumulation.

More recently, Lukyanova (1997) hypothesized that the enzyme–substrate–nucleotide interaction plays a critical role. According to this hypothesis, catecholamines–succinate–cAMP can be regarded as a functional unit, where succinate oxidation is regulated by catecholamines and, vice versa, succinate can stimulate catecholamine synthesis. In a similar manner, it can be hypothesized that the transmitter–substrate–nucleotide interaction is based on a complex of acetylcholine–oxoglutarate–GTP–cGMP.

Adaptation to hypoxia by an intermittent hypoxic challenge is associated with the expression of, and a shift toward, enzyme isoforms that can efficiently function in a mitochondrial environment with high concentrations of reduced equivalents as generated during hypoxia. This prevents inactivation of the MchEC and may constitute one of the adaptation mechanisms triggered by intermittent hypoxia. This hypothesis was supported by recent studies in rats (Serebrovskaya et al., 2001). A 30-min inhalation of a 7% O_2 gas mixture decreased ADP-stimulated liver mitochondrial respiration. However, the pattern of oxidation substrates was different from normoxic controls. In the presence of succinate, an increase of the Chance respiratory coefficient (state 3/state 4 respiration ratio) and the phosphorylation rate (P/O as ratio of ATP formed/O_2 consumed) and a decrease of O_2 uptake effi-

ciency with simultaneous activation of aspartate aminotransferase activity were observed. Simultaneously, oxidation of α-ketoglutarate, an NAD-dependent substrate, was inhibited. IHT caused reorganization of mitochondrial energy metabolism, favoring NAD-dependent oxidation and improving the protection against acute hypoxia. After 14 days of normobaric IHT (11% O_2, 15-min sessions with 15-min rest intervals, 5 times daily), in comparison to controls, acute hypoxic challenge in the presence of succinate resulted in an increase of the Chance respiratory coefficient, the ADP/O ratio and the phosphorylation rate, in activation of both aspartate and alanine aminotranferases, and in less lipid peroxidation. These findings indicated a more efficient use of oxygen under hypoxic conditions after IHT preconditioning.

One of the most significant peculiarities of adaptation to intermittent hypoxia is free-radical processes. As to the likely mechanisms of IHT effects, scientists considered that, while intermittent and sustained hypoxia had many aspects in common (Chizhov, 1992; Meerson, 1993), one obvious difference was that with intermittent hypoxia there were interspersed periods of normoxia. The periods of reoxygenation could lead to oxygen radical formation, which might be analogous to that occurring with normoxic reperfusion of transiently hypoxic or ischemic tissues (Belykh et al., 1992; Meerson et al., 1992a). If periods of hypoxia followed by normoxia led to formation of oxygen radicals, but if the hypoxia were much briefer than the periods of normoxia, and if the exposure sequence were repeated over days, then one might expect that antioxidant defenses could be enhanced much more effectively than in sustained hypoxia. In a relatively early study conducted in rats, Meerson et al. (1992) found that even the mild hypoxia of 2100-m altitude with continuous exposure for 30 d decreased both the content of lipid peroxidation products and tissue activity of the antioxidants superoxide dismutase and catalase. But when he exposed rats for 6 h/d for 30 d to the much more severe hypoxia of 5000 m, the tissue activity of these antioxidant enzymes increased and the content of peroxidation products remained normal (Table 1). His interpretation was that the mild continuous hypoxia had reduced the antioxidant defenses as a result of "atrophy because of inactivity," whereas the more severe intermittent hypoxia had enhanced the defenses.

Subsequently, the concept has been confirmed and extended. In one study, rats were given IHT by exposing them in a chamber to conditions similar to those at 5000 m for 5 h/d for either 14 or 42 d (Mankovskaya, 1993; Mankovskaia et al., 1997). When rats were then exposed to an acute hypoxic challenge of 7% oxygen, their skeletal muscle showed better maintenance of tissue P_{O_2} and better maintenance of calcium and magnesium ATPase activity than in control rats. In liver and brain mitochondrial membranes, their cytochrome c-oxidase and succinyldehydrase activities and activities of sodium and potassium ATPases were better maintained. In liver, brain, and heart, there was less lactate accumulation compared to controls. In a recent study rats were given shorter hypoxic exposures: 15 min five times daily for 14 d (Kurhalyuk and Serebrovskaya, 2001). When they were subsequently challenged by exposure to 7% oxygen, blood catalase and glutathione reductase activity were increased and malon dialdehyde concentration was half that of non-IHT controls. The findings were consistent with the concept that intermittent hypoxia stimulates increased antioxidant defenses.

Semenov and Yarosh (1991) demonstrated that hypoxic training of rats maintained at 4000 m, 7 h/d for 2 weeks, prevented pneumonia-induced activation of liver mitochondria lipid peroxidation. Semenov and Yarosh assigned Wistar rats to four treatment groups: (1) controls, (2) hypoxic training, (3) hypoxic training and pneumonia (induced within 3 d after hypoxic training), and (4) pneumonia without hypoxic training. Lipid peroxidation was assessed by comparison of diene conjugate, diketone, and total lipid concentrations; malondialdhyde formation; and katalase activity. Hypoxic training significantly increased the mitochondrial lipid to protein ratio 1.6-fold (group hypoxic training vs. controls). The lipid/protein ratios in rats exposed to hypoxic training and pneumonia were similar to the controls, while the mitochondrial lipid/protein ratio in rats exposed to pneumonia without hy-

TABLE 1. INFLUENCE OF SUSTAINED AND INTERMITTENT HYPOXIA ON LIPID PEROXIDATION AND ANTIOXIDANT ENZYMES ACTIVITY IN RAT TISSUES

	Sea Level	*Sustained Hypoxia (2100 m, 30 days)*	*Intermittent Hypoxia (barochamber, 5000 m, 6 hour/day, 30 days*
Heart			
MDA, nmol/mg protein	0.68 ± 0.03	0.61 ± 0.04	0.63 ± 0.03
Catalase, nmol H_2O_2/mg protein/min	162 ± 3	140 ± 2*	176 ± 8*
SOD, units/g protein	640 ± 41	416 ± 36†	712 ± 23*
Liver			
MDA, nmol/mg protein	0.77 ± 0.05	0.47 ± 0.03†	0.62 ± 0.04
Catalase, nmol H_2O_2/mg protein/min	580 ± 10	472 ± 27†	742 ± 29†
SOD, units/g protein	720 ± 30	500 ± 48*	1060 ± 39†
Brain			
MDA, nmol/mg protein	1.15 ± 0.05	0.66 ± 0.04*	1.03 ± 0.03
Catalase, nmol H_2O_2/mg protein/min	325 ± 9	283 ± 8*	410 ± 11†
SOD, units/g protein	1270 ± 12	850 ± 18*	1760 ± 16†

Source: Meerson, 1992b.
*$p < 0.05$ (according to sea level).
†$p < 0.01$ (according to sea level).

poxic training was 1.8-fold lower than in the control group. Markers of lipid oxidation in the groups exposed to hypoxia and hypoxia + pneumonia were not different from the controls. In comparison, pneumonia without hypoxic training caused a significant increase in lipid peroxidation. The study suggested that hypoxic training led to a rearrangement of mitochondrial energy metabolism, with increased lipid utilization and a more efficient link between oxidation and phosphorylation, as indicated in the study by significantly improved $\Delta ADP/\Delta O$ ratios and ADP phosphorylation in the rats exposed to hypoxia than in the controls.

Many of the surviving men who participated in the cleanup after the 1986 explosion at Chernobyl atomic station have nonspecific complaints, including malaise, easily induced fatigue, and loss of libido (Chaialo et al., 1991; Evdokimov et al., 1993; Gorpinchenko et al., 1999). Questions arose whether they might have continuing oxidant stress and, if so, whether such stress could be reduced by IHT. Some authors earnestly suggested significant activation of free-radical lipid peroxidation in individuals who were engaged in cleanup operations after the disaster (Chaialo et al., 1991; Sutkovyi et al., 1995). While it was not possible for us to answer these questions in humans with the methods available to us, the investigations gave potentially interesting findings (Serebrovskaia et al., 1996). Our approach was to compare 18 Chernobyl workers (ages 25 to 43 years) with 11 healthy men from Kiev. While there was considerable individual variability in the findings (Table 2), our indexes of oxidant stress before IHT were higher in the Chernobyl workers. We used a program of IHT: isocapnic, progressive, hypoxic rebreathing lasting for 5 to 6 min until inspired air O_2 reached 8% to 7%, with three sessions, separated by 5 min of normoxia, per day for 14 consecutive days. The use of IHT was accompanied by a decrease of spontaneous and hydrogen peroxide-initiated blood chemiluminescene, as well as considerable reduction of MDA content (Table 2). Of interest, more recent study on patients with bronchial asthma, who also were characterized by indexes suggestive of oxidative stress, have shown that similar IHT produced the increase of superoxide dismutase (SOD) activity by nearly 70%. This increase correlated with a decrease in MDA content ($r = -0.61$, $p < 0.05$) (Safronova et al., 1999; Serebrovskaya et al., 1999c). Although oxidant stress has been described in postradiation illness and bronchial asthma, the conditions are complex; there were in our cohorts large interindividual variations in the findings, and of course our correlations do not establish cause and effect. Therefore, although the findings are compatible with some

Table 2. Blood Chemiluminescence and Lipid Peroxidation in Healthy People and Clean-up Workers of Chernobyl Atomic Station after the Disaster

	Training Group (Chernobyl)			*Sham Group (Kiev)*		
Index	*Spontaneous Chemiluminescence (imp/min)*	*Induced H_2O_2 Chemiluminescence (imp/min)*	*MDA (nmol/L)*	*Spontaneous Chemiluminescence (imp/min)*	*Induced H_2O_2 Chemiluminescence (imp/min)*	*MDA (nmol/L)*
Before IHT	357 ± 44	719 ± 62	3.50 ± 0.40	221 ± 35†	481 ± 38††	2.13 ± 0.31†
After IHT	238 ± 35**	578 ± 51*	2.24 ± 0.16**	246 ± 43	440 ± 15†	2.30 ± 0.77

Source: Serebrovshaya et al., 1996.
*$p < 0.05$; **$p < 0.01$ (Chernobyl group vs. Kiev group).
$^{\dagger}p < 0.05$; $^{\dagger\dagger}p < 0.01$ (posttraining stage vs. pretraining).
Training group: 18 cleanup workers of Chernobyl Atomic Station (25 to 43 yr).
Sham group: 11 healthy residents of Kiev region (24 to 40 yr).

oxidant stress from radiation exposure in the Chernobyl workers and possible improvement with IHT, much remains to be done.

Thus studies in humans and in tissues have shown that adaptation to intermittent hypoxia induces increased antioxidant defenses, acceleration of electron transport in the respiratory chain, stabilization of cellular membranes, and Ca^{2+} elimination from the cytoplasm. These data served as the basis for IHT in the treatment of various diseases in which free-radical production might be anticipated, for example, bronchial asthma and post-Chernobyl syndromes.

Since adaptation to stress or exercise may be mediated, in part, by stimulating NO synthesis, the effects of intermittent hypoxia on NO metabolism were investigated by Russian and Ukrainian scientists. Recent studies have shown the following principal results: (1) adaptation to intermittent hypobaric hypoxia stimulates NO production in the organism; (2) excessive NO synthesized in the course of adaptation is stored in the vascular wall; (3) adaptation to hypoxia prevents both NO overproduction and NO deficiency, resulting in an improvement in blood pressure; and (4) effects of intermittent hypoxia on mitochondrial respiration are mediated mainly by NO-dependent reactions (Manukhina et al., 1999, 2000a,b; Malyshev et al., 2000; Ikkert et al., 2000; Smirin et al., 2000; Kurhalyuk and Serebrovskaya, 2001; Kurhalyuk et al., 2001b; Serebrovskaya et al., 2001). Because of the limited scope of this review, the interested reader is referred to these and other publications (Wolin et al., 1998; Reutov, 1999; Zenkov et al., 2000).

INDIVIDUAL VARIABILITY

One question has been whether IHT can provide insight into the marked individual variability in the response to, and the tolerance of, hypoxia, which is found within nearly every population. As has been shown among climbers on Mt. Everest, some humans are able to reach the summit of Mt. Everest breathing only the ambient air, while others are unable to tolerate much lower elevations even though they breathe supplemental oxygen as supplied by standard mountaineering equipment. CIS scientists have attempted a number of approaches to the fundamental question of individual variability in the response to hypoxia. These approaches are briefly indicated below with the hope that they may be of value in future research.

The presence of individual human variability to intermittent hypoxia has been described over several decades (Berezovsky, 1978; Berezovsky et al., 1981; Serebrovskaia, 1982, 1985; Berezovskii and Serebrovskaia, 1987, 1988; Berezovskii and Levashov, 2000a,b). The phenotypic and genotypic differences in the development of individual adaptations were determined by studying twins (Berezovsky et al., 1981; Serebrovskaia, 1982, 1985; Serebrovskaia

and Lipskii, 1982). It seems likely that estimation of human individual sensitivity to hypoxia is important for selection of individual IHT regimes during sport training or treatment of diseases. The special programs were developed to carry out hypoxic training according to individual reactivity (Berezovskii and Serebrovskaia, 1988; Berezovskii and Levashov, 1992, 2000a; Minyailenko and Pozharov, 1992; Lysenko et al., 1998; Tsvetkova and Tkatchouk, 1999). The mechanisms responsible for individual variability to IHT deserve continuing research, because they may provide clues to the general problem of human tolerance of hypoxia.

In the former Soviet Union and the CIS, the study of mechanisms has largely involved animal experiments, following the demonstration that even within one strain of rats there was substantial variability in hypoxic tolerance. Within one strain, some rats were able to survive 11,000 m of altitude for less than 3 min, while others survived more than 10 min (Berezovsky, 1978; Lukyanova and Korablev, 1982). Although there are several possible causes (ventilatory sensitivity, circulatory adjustments, acid–base balance, etc.) for such variability, much of the interest in the CIS has focused on the mitochondria.

For example, the rats that were more hypoxia resistant were found to have greater activity of the complex I mitochondrial enzyme than those with low tolerance (Lukyanova, 1997). In the brains of the more tolerant rats, maximum activity (V_{max}) and Km of NADH–cytochrome c oxidoreductase were significantly higher than in rats with low hypoxia tolerance (Table 3). The concept was that in the brains of less tolerant rats the enzyme would become more rapidly saturated with the substrate (NADH) and would oxidize the substrate at a slower rate. This may underlie the lower baseline activity of the NADH–oxidase pathway of substrate oxidation in the brains of the less tolerant rats (Lukianova et al., 1991; Lukyanova, 1996). Kinetic peculiarities of the mitochondrial enzyme complex I also underlie a lower oxidative efficiency of NADH–cytochrome c oxidoreductase in the brain of less tolerant rats exposed to hypoxia. Under these conditions, an increase in the NADH/NAD ratio could result in more rapid enzyme saturation with the substrate (NADH) and subsequent inactivation. If so, the limitation of the NADH–oxidase oxidative pathway would occur earlier and be more pronounced in the brains of less- versus more hypoxia-tolerant rats. One current working hypothesis, therefore, is that activity of mitochondrial complex I is a limiting pathway of oxidation, and where it is poorly developed, it contributes to hypoxia intolerance. Furthermore, the hypothesis is that complex I activity can be upregulated by IHT. These concepts deserve and require further investigation.

A somewhat different hypothesis has also been suggested, that the electron transport function of the myocardial respiratory chain in the NAD–cytochrome-b area is limited to a greater extent in animals poorly tolerant to hypoxia than in those that are not. In intolerant animals, even mild hypoxia leads to diminution of the oxidative capacity of the respiratory

TABLE 3. COMPARATIVE CHANGES OF KINETIC INDICES (V_{max} AND K_m) OF MITOCHONDRIAL ENZYMES IN BRAIN OF HIGH-RESISTANT (HR) AND LOW-RESISTANT (LR) RATS

Enzymes	*Kinetic indexes*	*Control LR/HR*	*LRad/LR after IHT*	*HRad/HR after IHT*	*LRad/HR after IHT*
NADH–cyt C oxidoreductase	V_{max}	0.43†	2.73‡	0.70*	1.67*
	K_m	0.22‡	1.43*	0.41†	2.16†
Succinate–cyt C reductase	V_{max}	0.99	1.20	1.00	1.09
	K_m	0.88	1.00	0.60†	1.19
Cytochrome oxidase	V_{max}	0.87	1.66*	1.38	1.06
	K_m	0.51†	1.99†	0.86	1.18

Source: Lukyanova, 1997.

HR, LR: control rats; Hrad, Lrad; adapted rats. Each group consisted of 20 white nonthoroughbred male rats, weight 200 to 250 g, on standard diet.

*$p < 0.05$; †$p < 0.01$; ‡$p < 0.001$.

chain and of ATP production and, as a consequence, to a suppression of the energy-dependent contractile function of the myocardium. In animals more tolerant of hypoxia, this process is less manifest and develops very slowly, which confirms the lesser role of NAD-dependent oxidation of substrates in the metabolism of the myocardium of these animals (Korneev et al., 1990). This concept also requires further exploration.

A different view, but one not mutually exclusive of the others, is that an inherently high resistance to acute hypoxia depends on predominance of the cholinergic limb of the autonomic nervous system (Vadzyuk, 1983). By contrast in animals with poor hypoxic tolerance, there is greater sympathetic than parasympathetic tone. The concept, as developed, suggests that there is differential selective oxidation of two substrates of the Krebs cycle: succinate versus α-ketoglutarate. Presumably, α-ketoglutarate can act within the Krebs cycle to enhance the cholinergic status of the organism (Doliba et al., 1993). In the study of Kurgalyuk and Shostakowskaya (1999), the role of α-ketoglutarate in liver mitochondrial enzyme activity was investigated. They found that in rats resistant to hypoxia the transamination enzymes and succinate dehydrogenase activities were much higher than in rats that poorly tolerated hypoxia, and α-ketoglutarate injections resulted in increased enzyme activity only in rats that were less tolerant. As a result, hypoxia tolerance increased more in those rats that initially had poor hypoxia tolerance. The blockade of *M*- and *N*-cholinoreceptors eliminated all α-ketoglutarate injection effects as well as the effects of adaptation to intermittent hypoxia (Kurhalyuk et al., 2001b).

Interestingly, IHT improves hypoxia tolerance in the more susceptible individual animals but to a lesser extent than in those that were naturally resistant (Vlasova and Torshin, 2001). CIS scientists have largely focused on cellular energy-related mechanisms as the basis of individual variability in hypoxic tolerance. Continued investigation is needed to establish whether these are primary causes of the variability, results of it, or both. Furthermore, experiments to select and successively breed the more resistant rats and experiments to do the same in susceptible rats could provide genetic enhancement of the individual variability within a given animal strain and thus be a tool for further study. As scientific barriers continue to fall, as past Russian and Ukrainian science becomes better known, as trust and cooperation increase among scientists worldwide, these issues will be aired and, I hope, solved.

SUMMARY

The above review has emphasized some of the extensive hypoxia research, more specifically on intermittent hypoxia, in the former Soviet Union and now in the CIS. Taken together these studies suggest that IHT induces increased ventilatory sensitivity to hypoxia in the absence of P_{CO_2} or pH changes; that it induces other hypoxia-related physiological changes such as increased hematopoiesis and decreased plasma volume and increase in alveolar ventilation and lung diffusion capacity; and that it may be useful in the management of certain disease states. The effects appear to be mediated, at least in part, through release of reactive oxygen species, which then induce an increase of antioxidant defenses. In addition, IHT appears to induce changes within mitochondria, possibly involving NAD-dependent metabolism, that increase the efficiency of oxygen utilization in ATP production. Studies from the Soviet Union and the CIS significantly contributed to the understanding of intermittent hypoxia and its possible beneficial effects and should stimulate further research in this direction in other countries.

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Different spellings of authors names are sometimes seen in English Medline.

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