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Etiology and Pathophysiology/Obesity Treatment

Hypoxia, energy balance and obesity: from pathophysiological mechanisms to new treatment strategies

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Summary

High altitude exposure is often accompanied by weight loss. Postulated mechanisms are a reduction of nutritional energy intake, a reduction of intestinal energy uptake from impaired intestinal function and increased energy expenditure. Beyond the field of altitude, there are good reasons for renewed interest in the relationship between hypoxia and energy balance. The increasing prevalence of obesity and associated comorbidities represent a major health concern. Obesity is frequently associated with sleep disorders leading to intermittent systemic hypoxia with deleterious cardiovascular and metabolic consequences. Hypoxic regions may be present within hypertrophic white adipose tissue leading to chronic systemic inflammation. Among the increasing number of people commuting to altitude for work or leisure, obesity is a risk factor for acute mountain sickness. Paradoxically, exposure to intermittent hypoxia might be considered as a means to lose body mass and to improve metabolic risk factors. Daytime exposure to intermittent hypoxia has been used to treat hypertension in former Soviet Union countries and is now being experimented elsewhere. Such intermittent hypoxic exposure at rest or during exercise may lead to improvement in body composition and health status with improved exercise tolerance, metabolism and systemic arterial pressure. Future research should confirm whether hypoxic training could be a new treatment strategy for weight loss and comorbidities in obese subjects and elucidate the underlying mechanisms and signalling pathways.

Keywords: Energy balance, exercise, hypoxia, obesity.

Abbreviations: AEE, activity related energy expenditure; AGRP, agouti-related peptide; AMPK, AMP-activated protein kinase; AMS, acute mountain sickness; BBB, blood brain barrier; BMI, body mass index; CCK, cholecystokinin; CNS, central nervous system; CSF, cerebrospinal fluid; DIT, diet induced thermogenesis; GLUT, glucose transporter; HIF1α, hypoxia-inducible factor-1α; IL-6, interleukin-6; MPAP, mean pulmonary artery pressure; NEAT, non-exercise activity thermogenesis; NPY, neuropeptide Y; OSA, obstructive sleep apnoea; $PaCO_2$, arterial CO_2 partial pressure; PaO_2, arterial O_2 partial pressure; PE, physical exercise; RMR, resting metabolic rate; TEE, total energy expenditure; TNFα, tumour necrosis factor-alpha; VEGF, vascular endothelial growth factor; WAT, white adipose tissue.

Introduction

Hypoxia influences energy balance. It is known since long that altitude exposure is often accompanied by weight loss. Overall, it seems that 5,000–5,500 m is an altitude limit beyond which maintenance of body mass and body composition are challenged. Postulated mechanisms for the disturbance of the energy balance are a reduction of nutritional energy intake, a reduction of intestinal energy uptake as a result of an impaired intestinal function and increased energy expenditure. Even though changes in intestinal absorption occur, malabsorption probably plays a minor role, the larger part of the energy deficit stemming from decreased energy intake (1).

There are several reasons for renewed interest in the relationship between hypoxia and energy balance. One is related to the global epidemic of obesity with its comorbities and health burden. Obesity can be defined as an excess of body fat stores. Body mass index (BMI; weight height^{-2} in kg m^{-2}) is generally used as a proxy for body composition. The World Health Organization classifies a BMI > 25 as overweight, and a BMI > 30 as obese (2). Today, more than 1.4 billion adults are overweight of which more than 400 million are obese (2). Obesity represents a major health burden because, among others, it is accompanied by an increased risk for insulin resistance, diabetes, hypertension, cardiovascular diseases and various cancers. Recent data point to an important role for hypoxia in obesity, likely because of regions of hypoxia in hypertrophic white adipose tissue leading to a state of chronic mild inflammation (3,4). Also, obstructive sleep apnoeas (OSA), a very frequent problem in overweight and obese subjects, are characterized by intermittent episodes of systemic hypoxia with dangerous cardiovascular and metabolic consequences (5,6). In view of the increased obesity prevalence, among the millions of people commuting to altitude for work or leisure, increasingly many are likely to be overweight or obese. Because of the mentioned effects, hypoxia may thus perhaps pose more problems for obese subjects than for non-obese subjects, over more since obesity appears to be a risk factor for acute mountain sickness (7–10).

But paradoxically, exposure to intermittent hypoxia is also being experimented as a means to lose body mass or to improve metabolic risk factors. Even though the paroxystic exposure to hypoxia in OSA seems causally related to the development of systemic hypertension (5), daytime intermittent hypoxia as means of treatment for hypertension has been common in former Soviet Union countries for decades and is now also being experimented elsewhere (11). Recent preliminary data from a controlled trial where subjects engaged in 8 weeks training with three 90-min exercise sessions at 60% of maximum heart rate in a normobaric room with either 21 or 15% O_2, provide some indication that exercise sessions in hypoxia might induce slightly greater weight loss in overweight subjects as compared to exercise alone (12). Haufe *et al.* (13) tested in healthy subjects the hypothesis that training in hypoxia has more effect than training in normoxia with regard to several metabolic risk factors. Despite a lower absolute workload, they found that hypoxic training was better than normoxic training. Similar as for hypertension (11), hypoxia may thus be a two-sided sword for obesity and its comorbidities, potentially playing a role both in the pathogenesis and therapy of the disease.

The purpose of this review is to summarize current understanding of the role of hypoxia in energy balance and pathogenesis of obesity-related pathology and the potential of hypoxia as a therapeutic adjunct for treatment of obesity.

Energy balance and hypoxia

Energy balance

Obesity results from a positive energy balance when energy intake is greater than energy expenditure. Normally, the regulation of energy balance is extraordinarily precise, adapting energy intake to energy expenditure in order to keep body mass at a given 'set-point', at least when physical activity level reaches the level of international recommendations, i.e. 30–60 min of moderate physical activity each day at an intensity of 3–6 metabolic equivalents (14). For an average person, just a mere 1% error in the energy balance theoretically leads to ~1 kg change in fat mass in 1 year, which represents a 10-kg increase in fat mass over a decade for a ~25 kcal excess daily energy intake (a little more than one sugar lump d^{-1}).

Energy intake represents the amount of metabolizable calories provided by food ingestion each day and is therefore determined by the diet composition. Energy expenditure can be partitioned into resting metabolic rate (RMR), diet induced thermogenesis (DIT) and activity related energy expenditure (AEE). RMR is largely function of body size and composition and represents the energy cost of the organism not moving or digesting; DIT represents the energy cost of digestion (~10% of total energy expenditure [TEE]); and AEE is the variable part of TEE that corresponds to the energy expenditure from physical activity. AEE can be partitioned into physical exercise (PE) and non-exercise activity thermogenesis (NEAT). Spontaneous physical activity, which is part of NEAT, contributes significantly to TEE.

Altitude has a potentially important impact on energy balance and body composition; many studies have reported loss of body mass during altitude sojourns (for reviews see (1,15–17)). Hypoxia clearly plays a key role, but especially in field conditions (climbing expeditions, high altitude

trekking) the interplay between hypoxia and changes in dietary habits, activity patterns, cold and exposure to foreign pathogens is not easy to disentangle (1).

Resting metabolic rate

In contrast to newborns (18), adult humans acutely exposed to hypoxia show an increase in RMR (19,20), even though at altitude the interplay between cold and hypoxia for the observed increase is not fully clear (21). Beta-blockade partially counters the increase in RMR (22). The reason for the increase in RMR is thus potentially related to the increase in sympathetic activity, but possibly also to thyroid activity (15). Another potential player may be interleukin-6 (IL-6) which has been reported to increase RMR (23,24) and of which plasma levels increase in hypoxia (see below). During the initial phase of altitude exposures between 3,500 and 5,000 m, increases in RMR between 10 and 28% that partially subside with time have been reported (17). In military settings at 4,300 m, an imposed increase of daily energy intake by an amount equivalent to the increase in RMR allowed to counter the major part of the energy deficit (19). In relatively comfortable conditions and with access to a good choice of palatable food items, it may be possible to maintain body composition up to 5,000 m (25). At higher altitudes loss of body mass from negative energy balance seems inevitable. It is not known if with prolonged exposure (months, years) RMR returns to low altitude levels.

Activity energy expenditure

In animals, acute hypoxia generally leads to a reduction in physical activity. Energy expenditure in men while climbing Mount Everest was 14.7 MJ d^{-1} compared with 12.1 MJ d^{-1} for similar individuals while staying in a hypobaric chamber at 7,000–8,000 m (1,26,27). Such levels of energy expenditure correspond to active living at sea level. The perception of effort at altitude is high, but the actual levels of energy expenditure are in fact rather low because of the reduction in aerobic capacity so that on the summit of Everest slow walking corresponds to maximum exercise capacity. Energy intake on Mount Everest and in a hypobaric chamber at 7,000–8,000 m was similar, 7.9 ± 1.6 and 8.3 ± 1.9 MJ d^{-1}, respectively, and energy deficit on Mount Everest was thus on average 6.8 ± 1.7 MJ d^{-1} compared with 3.9 ± 1.4 MJ d^{-1} in the hypobaric chamber. The rate of loss of body mass was therefore twice as large during altitude climbing compared to being sedentary at the simulated altitude of 7,000–8,000 m, i.e. respectively, –0.22 ± 0.06 kg d^{-1} and –0.09 ± 0.05 kg d^{-1} (1). Energy intake is therefore the dominant determinant of loss of body mass during prolonged hypoxia and is influenced by the (field) settings, energy intake being lower on a real mountain compared to a hypobaric chamber. The loss of body mass from prolonged exposure to high altitude in expedition settings is predominantly fat mass, but, especially in lean subjects, also includes muscle mass (28–31), independently from physical activity levels (1,17,32).

Fluid balance

A hallmark of maladaptation to altitude resulting in altitude sickness is fluid retention (33). Conversely, adequate adaptation to altitude is accompanied by fluid loss (34,35). Provided there is proper acclimatization, about 1 to 2 kg of body mass loss at altitude is probably from fluid. On acute return from a hypobaric chamber simulated climb of Everest, body mass was restored by 63% of the loss within 4 d, suggesting physiological fluid retention upon return to sea level (36).

Malabsorption

It has been proposed that above 5,500 m hypoxia-induced malabsorption contributes to the negative energy balance at high altitude, but the evidence is weak. The only field evidence for reduced energy digestibility comes from the American Research Expedition to Mount Everest, when Boyer and Blume reported increased fat levels in faeces collected from climbers at 6,300 m (28). Other high altitude studies that actually measured food energy digestibility using bomb calorimetric measurement of faeces energy content, showed digestibility levels between 85 and 96% up to 6,500 m in the field as well as during a simulated Everest climb (26,27,37). There are changes in gut function affecting for example intestinal sugar transport, but these changes have no major impact on overall energy digestibility (1,15,38). Intestinal flora changes during a mountaineering expedition to the Himalayas might explain occasional malabsorption. Kleessen *et al.* (39) reported changes in intestinal flora and signs of immunological stress in seven climbers in field conditions, of whom five had episodes of diarrhoea. They speculated that hypoxia *per se* had an effect on intestinal flora composition, but could not distinguish between altitude, exertion, changes in nutrition and exposure to different bacterial strains while in the Himalayas. It thus would seem plausible that if in actual field conditions changes in intestinal flora lead to clinical or subclinical infection, intestinal malfunction may become apparent and sometimes lead to malabsorption.

Appetite

Overall, the negative energy balance in hypoxia seems to be largely due to a reduction in energy intake from a lack of appetite. What regulates appetite and what influence has hypoxia? The increasing prevalence of obesity has led to

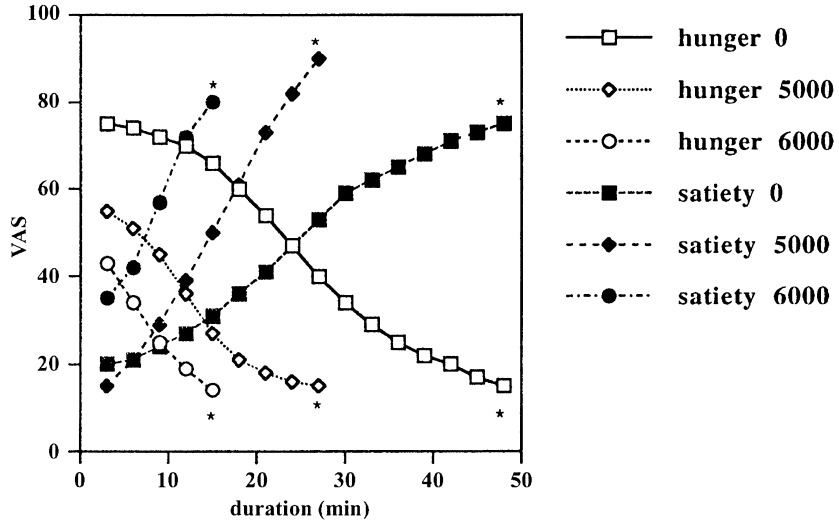

Figure 1 Appetite profile (hunger and satiety) during dinner at normoxia (0) and at stimulations of 5,000 and 6,000 m. Visual analogue scale (VAS) ratings at every 3 min are shown. * significantly different from the level at 3 min ($P < 0.001$) (from Westerterp-Plantenga *et al.* (36)).

major efforts to unravel the mechanisms regulating appetite, food intake and energy balance and understanding has improved considerably (for reviews see (40–44)). The overall picture is one of complexity and redundancy. Cross-talk between the gastrointestinal system, adipose and muscle tissue, and the central nervous system (CNS) lead to food ingestion behaviour aimed at an energy intake appropriate for varying energy needs. Eating behaviour is not only function of physiological parameters but is also under the effect of strong social influences. The physiology of food intake and its determinants is complex. The hypothalamus plays a key role with the arcuate nucleus being a central player, integrating neural, metabolic and endocrine information about energy intake and expenditure. The periphery generates episodic and tonic signals carrying information on the physiological state of the organism. For example, in response to fasting the (empty) stomach releases ghrelin, an orexigenic hormone. Various satiety-inducing compounds are released postprandial by the gastrointestinal system, such as glucagon-like peptide-1, pancreatic polypeptide, peptide YY, cholecystokinine (CCK) and many other compounds. Tonic signals include leptin, released mainly by adipose tissue, and insulin mainly by the pancreas, even though the latter also fluctuates according to prandial state and sugar content of dietary intake. Leptin and insulin influence body mass regulation by stimulating the release of anorexigenic molecules in the hypothalamus like propiomelanocortin, neuropeptide Y (NPY) and agouti-related peptide (AGRP), but probably also by modulating indirectly the sensitivity of the brain to satiety signals. Many other compounds have been identified but the orchestration of all of these in the regulation of energy balance is still far from completely understood. An additional level of complexity is added by the fact that many of the molecules playing a role in energy intake regulation such as CCK, corticotrophin-releasing hormone, neuromedin U, NPY, leptin, AGRP, orexin-A and ghrelin also have effects on energy expenditure through their influence on NEAT (reviewed in (45)).

Energy and protein intake at high altitudes may be reduced by 20–40% (46,47). Differences in food availability (both quantitative and qualitative) can partly explain differences in energy intake between high altitude and comfortable sea level conditions. However, offering palatable food and encouraging food consumption may only partially prevent weight loss in subjects exposed to high altitude (19). Westerterp-Plantenga *et al.* (36) reported changes in appetite profile during a 31-d simulated ascent to the equivalent of the summit of Mount Everest in a hypobaric chamber. Subjects lost 5 kg on average, despite access to palatable food and absence of cold exposure, stress or overexertion. This was accompanied by reduced appetite, with less hunger and a more rapid increase in satiety (Fig. 1). These results suggest that prolonged hypoxic exposure leads to reduced food intake by changing the appetite profile and the attitude towards eating. The mechanisms underlying these effects are still to be clarified (see section *Hypoxia and (an)orexigenics*).

Energy balance sensing

A key player in the regulation of energy balance seems to be the signalling protein AMP-activated protein kinase (AMPK, for a review see (48)). AMPK is activated by metabolic stress disturbing energy balance, when the ATP/AMP ratio decreases, either through decreased ATP production or increased ATP consumption. Modulation of the ratio can be induced by lack of energy substrate or hypoxia. Glucose sensing cells (β-cells in the pancreas and glucose regulated neurons in the hypothalamus) use

AMPK activation to signal glucose decreases. In the glomus cells of the carotid body and in the smooth muscle cells of the pulmonary artery AMPK activation is used to signal hypoxia. Interestingly, AMPK activity regulation can also be modulated by adipokines. In the muscle, leptin and adiponectin activate AMPK and increase glucose uptake and fatty acid oxidation. Adiponectin activates AMPK in the liver stimulating fatty acid oxidation and inhibiting glucose production whereas resistin has opposite effects. Other anorexigenic agents as insulin, melanocortin receptor agonists and high glucose levels also inhibit AMPK in the hypothalamus, whereas orexigenic agents such as agouti-related protein, ghrelin and cannabinoids activate AMPK in the hypothalamus. At the whole organism level, AMPK activation causes a switch from the anabolic state (synthesis and storage of substrate, increased cell growth) to a catabolic state oxidizing substrate and inhibiting cell growth and proliferation (48).

Hypoxia and (an)orexigenics

Do hypoxia and/or altitude have an impact on any of the mentioned molecules or their effects? Much remains to be investigated but leptin may be a candidate. Mainly produced by adipose tissue, it acts on target receptors in the hypothalamus lowering food intake. But leptin should not be considered simply as an anorexigenic only. It is also produced elsewhere and exhibits functional pleiotropy, for instance by acting on insulin resistance by promoting fat oxidation and by inhibiting lipid synthesis (49), by inducing angiogenic processes (50) or by influencing cell proliferation and apoptosis (51). Leptin is also tightly connected with inflammatory processes: while cytokines such as IL-6 and tumour necrosis factor-alpha (TNFα) promote leptin production, leptin also enhances the production of inflammatory cytokines (52,53) which may be important in the context of hypoxia and obesity (54). Several studies suggest that hypoxia directly stimulates leptin release under controlled experimental conditions (55,56), whereas leptin levels may paradoxically decrease in response to certain physiological conditions associated with altitude such as increased physical activity levels, weight loss, sympathetic activation and cold exposure (57–60). Results in leptin-receptor-deficient mice showing a reduction in caloric intake under hypoxic conditions (61) suggest that other pathways than leptin may play a role in the hypoxia-induced anorexia. A recent animated debate in the Journal of Applied Physiology on whether altitude exposure influences leptin levels clearly shows that we don't know yet (62).

The molecule CCK is traditionally known as a short-term satiety factor involved in meal size reduction and termination, also initiating a behavioural satiety sequence. Bailey *et al*. (63) investigated whether CCK plays a role at altitude (5,100 m) and during exercise. Resting plasma CCK was markedly increased on the morning of the second day at altitude. CCK response was not different in five subjects with anorexia, but a more pronounced increase in resting CCK was found in subjects with acute mountain sickness (AMS). More recent results from the same group cast some doubt on a role for CCK in anorexia at high altitude. Although acute normoxic exercise seems to be a potent CCK stimulus, acute hypoxic exercise actually resulted in a decrease in plasma CCK (64). Furthermore, CCK also influences physical activity levels negatively and the net effect of CCK on long-term energy balance remains uncertain (45). Little is known about other (an)orexigenic molecules and their role in energy balance in hypoxia. Changes in NPY, ghrelin, galanin and CCK (63,65,66) have been suggested to be responsible for anorexia at high altitude, but the mechanisms possibly underlying anorexia during hypoxic exposure remain mostly to be elucidated.

Interleukin-6

One important potential player in hypoxia is perhaps IL-6. Muscle tissue is a source of signalling molecules called myokines and muscle is today regarded as an endocrine organ. An important myokine is IL-6 (67). IL-6 was generally known as an inflammatory cytokine potentially playing a role in insulin insensitivity. In their review on IL-6 production in the muscle, Pedersen and Febbraio (67) present evidence that IL-6 released by muscle may have a different role as IL-6 from other sources and may actually be an anti-inflammatory cytokine, antagonizing inflammatory cytokines like TNFα and IL-1b. IL-6 is produced in various places of the body including the brain, paratendinous tissue, adipose tissue and muscle tissue. The IL-6 produced during exercise comes largely from activated muscle fibres and leads to high plasma peak levels post-exercise that rapidly subside. High physical activity levels result in low basal IL-6 levels while high basal IL-6 levels accompany low levels of physical activity. The muscle contraction induced IL-6 gene expression is related to the intensity and duration of the exercise, the mass of muscle recruited and endurance capacity. Reduced muscle glycogen content increases p38 mitogen-activated protein kinase activation and it seems likely that this in turn up-regulates transcription of IL-6. IL-6 can activate the energy state sensing protein AMPK. Like leptin, IL-6 can activate AMPK in skeletal muscle and adipose tissue, increasing glucose uptake. Overall, it thus seems that exercise induced IL-6 has rather positive effects on metabolism. The hypothesis that IL-6 induces insulin resistance is thus challenged, not in the least because muscle contraction increases IL-6 while insulin sensitivity is improved. In fact, IL-6, through the gp130 receptor can activate pathways that have both anti-obesogenic and insulin-sensitizing effects. Recent data

in rats again indicate that IL-6 enhances insulin sensitivity (68). The authors tested the hypothesis that phasic IL-6 infusion, like encountered during PE, would have a beneficial effect whereas continuous IL-6 infusion, like encountered in chronic inflammation, would not. Interestingly, both had a beneficial effect, again corroborating the observation in humans that IL-6 is improving insulin sensitivity (69). IL-6 has also been recognized as a novel lipolytic factor and increases fat oxidation (see for a review (69)).

On the other hand, when administered (intravenous or subcutaneous) to animals or humans, IL-6 induces sickness behaviour (fatigue, lethargy, loss of appetite, reduction in physical activity levels) (70–72). For example, in a controlled double blind study the infusion of rhIL-6 made subjects feel tired, inactive and less capable of concentrating (72). Furthermore, high basal IL-6 levels have been related to major depression episodes in humans (73) and treatment with a humanized antibody directed against IL-6 and soluble IL-6 receptor (sIL-6r; tocilizumab) has repeatedly shown to be very effective in the treatment of several debilitating autoimmune illnesses like rheumatoid arthritis also alleviating sensation of fatigue and improving appetite (74).

Hypoxia increases IL-6 both in normal subjects at altitude (75,76) and in patients with hypoxemia at low altitude (77). The levels of IL-6 seem inversely correlated to the arterial oxygen saturation (75,77). In hypoxia, IL-6 knockout mice show less sickness behaviour than wild-type mice (70).

Apart from headache, other hallmark symptoms of AMS are anorexia and lassitude/fatigue (78). Typically energy intake is reduced during acclimatization to altitude (see Fig. 2) (79). But also in acclimatized subjects hypoxia is accompanied by reduced appetite (see Fig. 1) (36). It thus is tempting to speculate that that the syndrome of lethargy and anorexia observed during hypoxia exposure might be related to hypoxia-induced increased IL-6.

Lundby and Steensberg (80) looked at the effect of acute and chronic hypoxia on the exercise induced increase in plasma IL-6 levels and found a synergistic effect of hypoxia and exercise, independent of catecholamine levels, so that IL-6 were similar in hypoxia and normoxia at the same relative workload, and higher in hypoxia at the same absolute submaximal workload.

In a double blind controlled study, Robson-Ansley *et al.* (81) infused rhIL-6 in healthy subjects and showed that it led to impaired exercise performance. After exercise, the levels of prolactin, adrenocorticotropic hormone and cortisol were higher in the rhIL-6 infusion trial. The same authors reported that prolonged endurance exercise over several days leads to persistent increase in plasma levels of the sIL-6r in parallel to an increase in fatigue sensation (82). Data from Nybo *et al.* (83) would argue against a role of IL-6 in central fatigue. They looked at cerebral arterio-

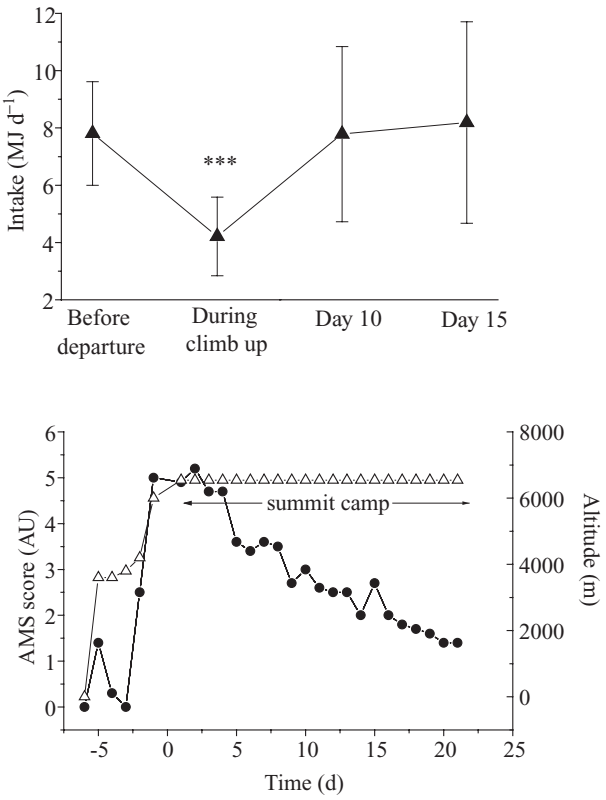

Figure 2 Energy intake (upper panel) and score for acute mountain sickness (AMS, lower panel) in 10 subjects during a 21-stay at 6,524 m. * significantly different from the other time point ($P < 0.001$) (from Westerterp *et al.* (79)). △, altitude in meters; ●, Lake Louise AMS score in arbitrary units.

venous differences of IL-6 and found a net brain IL-6 release during prolonged exercise in humans that appeared to be influenced by the duration of exercise rather than by an increase in body temperature.

Interestingly, recent data indicate that IL-6 plays a role in pulmonary artery remodelling. Steiner *et al.* (84) used a mouse model overexpressing IL-6 and found vasculopathy typical of pulmonary arterial hypertension patients, increased pulmonary artery pressure and right heart loading, all of which were exacerbated by hypoxia. In another mouse model, lacking IL-6, less hypoxic pulmonary vasoconstriction was reported compared to wild type (85). It can thus be speculated that hypoxic pulmonary arterial vasoconstriction from IL-6 plays some role in the pathogenesis of high altitude pulmonary oedema.

Blood brain barrier (BBB)

An important aspect that has not yet received sufficient attention is the fact that increased plasma concentrations of circulating adipokines and other compounds do not necessarily translate to changes in the CNS. In fact the BBB,

formed by the monolayer of endothelial cells of the brain vessels joined by tight junctions and layered on a continuous basement membrane lined by astrocytic end-feet and pericytes, is not readily permeable for many molecules (86). The BBB has a saturable transport system for leptin; several BBB receptors (ObRa, ObRb, ObRc, ObRd) and a soluble receptor ObRe are involved. Transport over the BBB of IL-6 is also saturable, and IL-6 may be transported both ways, into and out-of the CNS (83,86). Steensberg *et al*. (87) reported that at rest, cerebrospinal fluid (CSF) levels of IL-6 were twofold higher than plasma levels. During exercise, plasma IL-6 increased as expected. However, the concentration of IL-6 in CSF did not change with exercise and was below corresponding plasma level, suggesting that the CSF pool is indeed segregated from that in blood. Studies reporting changes in plasma concentrations of compounds playing a role in energy balance correlating these to changes in energy intake or expenditure must therefore be carefully interpreted.

The role of hypoxia in obesity

Hypoxia and white adipose tissue

White adipose tissue (WAT), once thought to be just a highly efficient means for energy storage, is now known as an active endocrine organ releasing important regulatory adipokines such as leptin (for reviews see (3,4)). Excess adipose tissue as in obesity is characterized by a state of permanent mild inflammation with increased circulating levels of inflammatory markers such as C-reactive protein, haptoglobin, IL-6, monocyte chemo-attractant protein-1, plasminogen activator inhibitor-1 and TNFα. Recently, a 'hypoxia hypothesis' was forwarded, which proposes that adipose tissue hypertrophy would lead to localized hypoxia inducing AMPK activation and induction of local inflammation (3). Circumstantial evidence comes from the observations that the proportion of cardiac output and blood flow to WAT is not increased in the obese, that obese do not show the postprandial increase in blood flow to adipose tissue seen in the lean, and that hypertrophied adipocytes can become so large (150 to 200 μm in diameter) that normal diffusion for oxygen is impaired. Direct evidence comes from the measurement of localized hypoxia in adipose tissue in obesity by means of oxygen-meters and hypoxia-sensitive chemical probes, demonstration of up-regulation of hypoxia-activated genes like the hypoxia-inducible factor-1 (HIF1α), vascular endothelial growth factor (VEGF), glucose transporter (GLUT1), heme-oxygenase and 3-phosphoinositide-dependent protein kinase-1 and increased levels of tissue lactate indicating Pasteur effect (4).

HIF-1α is thought to play a pivotal role in the response to hypoxia within WAT as in other tissues. Some 70 genes are currently identified as being hypoxia-sensitive through HIF-1α and encompass those encoding several proteins involved in glucose and energy metabolism, cell proliferation, apoptosis and angiogenesis (88). While in normoxic conditions HIF-1α is consistently synthesized and degraded, hypoxic conditions such as within adipocytes promote HIF-1α stabilization and translocation. HIF-1α is expressed at higher levels in adipose tissue of obese rodents as compared to lean, and its mRNA has been reported to be up-regulated in fat tissue and infiltrating macrophages of obese humans. This increase in HIF-1α expression may be involved in several hypoxic responses in WAT, including increased GLUT1 concentration, expression and secretion of inflammation-related adipokines, production of the angiogenic factor VEGF and insulin resistance (3).

The adipokines produced in hypoxic adipocytes are involved in several important physiological and metabolic processes through autocrine, paracrine and endocrine mechanisms. Adipokines influence insulin sensitivity, glucose homeostasis, angiogenesis, inflammation, immunity, food intake and energy expenditure (89). Leptin and adiponectin are the most prominent protein hormones secreted by adipocytes and are increased and reduced, respectively, in obese patients. The link between hypoxia, adipokines, inflammation and energy balance is complex but probably plays a key role in obesity physiopathology (89–91).

Obesity, obstructive sleep apnoea and hypoxia

OSA is a disorder in which loss of pharyngeal muscle tone at sleep onset causes recurrent pharyngeal collapse and temporary cessation of breathing (5). This causes repeated episodes of hypoxia and carbon-dioxide retention, interrupted by short arousals when muscle tone increases again and airflow is restored, followed by the next episode upon sleep onset. The hypoxic component is thought to be the major mechanism responsible for OSA cardiovascular, metabolic and cerebral consequences (92–94). The desaturation-reoxygenation sequence typical of OSA leads to oxidative stress, with production of reactive oxygen species (95), contributing to the development of systemic inflammation (96). OSA is generally defined as five or more apnoeas–hypopnoeas per hour of sleep (i.e. the apnoea–hypopnoea index). OSA is a very common clinical condition, occurring in at least 4% of males and 2% of females. Given the rapidly rising incidence of obesity, which is the most important risk factor for OSA, one can expect that the prevalence is increasing. OSA increases the risk for systemic hypertension. Repetitive stimulation of the sympathetic system through the carotid chemoreceptors results in the increase in blood pressure. Since the sympathetic nervous system is also activated in chronic hypoxia such as when travelling to high altitude (97–101) it can be expected that

OSA patients at altitude would be at increased risk as compared to low altitude. In healthy subjects exposed to low inspiratory oxygen, the hypoxic ventilatory response induces respiratory alkalosis. The combination of reduced arterial O_2 (PaO_2) and CO_2 ($PaCO_2$) partial pressures may lead to oscillations in breathing, especially during sleep, which may take the form of central apnoeas. These central apnoeas are different from the obstructive ones in OSA in that in the latter high $PaCO_2$ accompanies the low PaO_2. OSA patients who travel to high altitude might thus be at risk from a combination of central and obstructive apnoeas (102). Patients, who live above >2,400 m in Colorado underwent diagnostic sleep studies at their home elevation and at 1,370 m, had less apnoeas at low altitude indicating that this problem is probably real but insufficiently recognized (103).

In a recent review, Ryan and McNicholas (6) propose that the unique short intermittent hypoxia/hypercarbia in OSA would preferentially activate nuclear factor κB mediated inflammatory pathways over adaptive HIF-1α dependent pathways. The intermittent hypoxia associated with OSA was found to induce increased resting levels of IL-6 since treatment with continuous positive airway pressure decreased IL-6 levels by 46% and abolished diurnal variation of serum levels present before treatment (104).

Obesity and altitude

Obesity and altitude sickness

Obesity seems to be a risk factor for AMS. Data from the Qinghai-Tibet railroad construction suggest that obese persons are more susceptible to AMS, the incidence being almost three times higher in the obese than in subjects with normal BMI (97% vs. 37%) (9). Hirata *et al.* (10) found that lean subjects (BMI < 22) were less susceptible to AMS at 5,150 m than those who are standard or obese, the incidence of AMS being 22, 54 and 70%, respectively. Kayser (7) showed that male trekkers who suffered AMS around the Thorong Pass (5,400 m) had significantly higher BMI than those who were not sick. Ri-Li *et al.* (8) found that obesity predisposes to AMS in conditions of simulated hypoxia. It is not clear how obesity predisposes to AMS, and relative hypoventilation has been proposed to play a role, in relation to a higher incidence of sleep hypoxemia (35). Interestingly, moderately obese subjects rather have an increased chemosensitivity to hypoxia and hypercapnia when compared to normal weight subjects (105).

Obese persons appear to have more pulmonary hypertension than normal subjects at the same altitude (9). Even at a moderate altitude of 2,240 m, 20 obese subjects had a mean pulmonary artery pressure (MPAP) of ~30 mmHg, higher than that measured in normal weight subjects (~15 mmHg) at the same altitude and higher than in normal weight Peruvians (~22 mmHg) living at the higher altitude of 3,730 m (106). Wu *et al.* (9) also reported, at altitudes between 4,630 and 4,905 m, that subjects with a BMI > 28 had even higher MPAP (~31 mmHg) than those with a BMI of 25–27 (~24 mmHg) and subjects with a BMI of 22–24 (~22 mmHg) (Fig. 3). Obesity or BMI is not known as a risk factor for high altitude pulmonary oedema even though a recent case report in a subject with Down syndrome, OSA and a BMI of 38 would suggest that it may be (107).

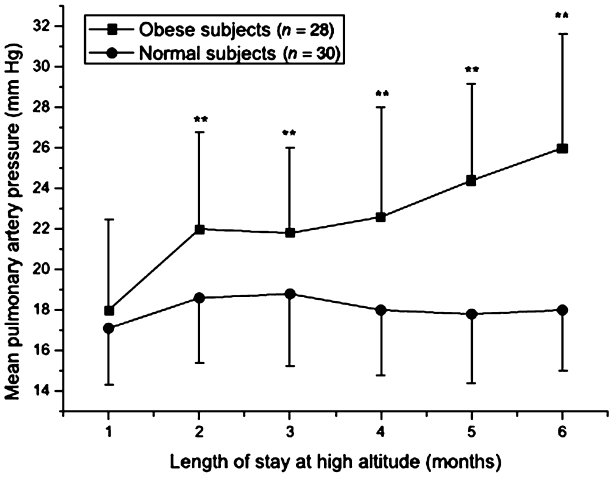

Figure 3 Pulmonary artery pressure in obese and normal subjects at altitude. * significantly different compared to baseline ($P < 0.01$) (from Wu *et al.* (9)).

It can be speculated that apart from exaggerated nocturnal hypoxia exposure, the increased levels of IL-6 in obese subjects may play a role in their increased sensitivity to AMS as well as their exacerbated MPAP response to hypoxic exposure, but the exact mechanisms that predispose obese subjects to altitude maladaptation remain to be clarified.

Obesity in populations living at high altitude

Investigating populations living at high altitude may help to elucidate the mechanisms associated with hypoxia adaptation or maladaptation. Some studies investigated body mass and metabolic status in populations living at high altitude (108–111), but most of them have no control population or do not take into account major confounders such as differences in lifestyle. Santos *et al.* (109) for instance reported in an Aymara population living at altitude (>2,000 m) in Northern Chile a relatively high prevalence of BMI ≥ 30 (12.8% in males and 23.5% in females) similar to other populations living at sea level in south America, but a low prevalence (1.3% in males and 1.7% in females) of type 2 diabetes mellitus. Differences in lifestyle and especially higher levels of physical activity in such rural

populations living at altitude may explain the lower prevalence of type 2 diabetes mellitus. Voss *et al.* found in a USA-wide representative sample of >400,000 subjects that after controlling for urbanization, temperature category and behavioural and demographic factors, male and female Americans living < 500 m above sea level had 5.1(95% confidence interval [CI] 2.7–9.5) and 3.9 (95% CI 1.6–9.3) times the odds of obesity, respectively, as compared with counterparts living > 3,000 m (112). Another recent study investigated the effect of altitude on obesity prevalence by comparing BMI in Tibetans living at varying altitudes of 1,200, 2,900 and 3,600 m in Nepal and Tibet (111). There was a significant inverse relationship between BMI and altitude of residence. This effect of altitude remained significant when controlling for calorie intake and physical activity, suggesting an effect of altitude *per se*. Although the reasons for this altitude effect remain to be elucidated, it is conceivable that energy balance in populations living at high altitude is influenced by hypoxia as described above.

Hypoxia as a treatment?

Altitude sojourns

Altitude exposure influences energy balance on both sides. Physical activity levels tend to decrease while energy intake is reduced out of proportion. It thus would seem that altitude sojourns might be of therapeutic use for obese subjects. Wu *et al.* (9) found that obese persons working at altitudes above 4,000 m for 3 to 5 months lost weight, reaching near normal body mass. Boyer and Blume (28) reported that subjects with a higher BMI lost more weight at altitude, a finding also reported by others (8) and known to occur in animals since the 1950s (113). Trekking or working at altitude, combining hypoxia and exercise, is therefore perhaps an excellent way to lose excess body mass. On the other hand, since obesity is accompanied by increased prevalence of AMS, it is possible that the weight loss is partly due to altitude illness. Furthermore, since subjects with OSA may experience an aggravation of their problem by the synergistic effect of central apnoeas from low inspired oxygen, some reservation remains (102). Overall, it appears that if moderate excess body mass does not pose any particular disadvantage at high altitude, obese subjects seem to be at increased risk at altitude, a risk that might be exacerbated upon presence of other comorbidities like cardiovascular disease.

So far, few studies have investigated the therapeutic use of actual altitude exposure in obese. Schobersberger *et al.* (114) brought patients with metabolic syndrome for 3 weeks to 1,700 m and found improvements in systemic arterial pressure and several metabolic indices, but could not discriminate between altitude-specific and exercise effects because of the lack of a control group. Lippl *et al.* (115) reported in obese subjects immediately at the end and 4 weeks after a 1-week stay at 2,650 m, decreased body mass and diastolic blood pressure and increased basal metabolic rate and leptin levels, but again there was no control group. In both studies, subjects appeared to tolerate such relatively modest altitude levels without major symptoms of cardiovascular or metabolic problems. Further randomized controlled studies are needed to clarify the impact of altitude stays and concomitant changes in diet and physical activity on body mass and comorbidities in obese subjects.

Intermittent hypoxia

Instead of continuous hypoxic exposure such as at altitude, intermittent hypoxic exposure may be another option for obese subjects (116). In a model of diet-induced obese mice, it was shown that compared to normoxia, intermittent hypoxic exposure reduces body mass, blood sugar, blood cholesterol and liver fat cells and increases serum leptin,

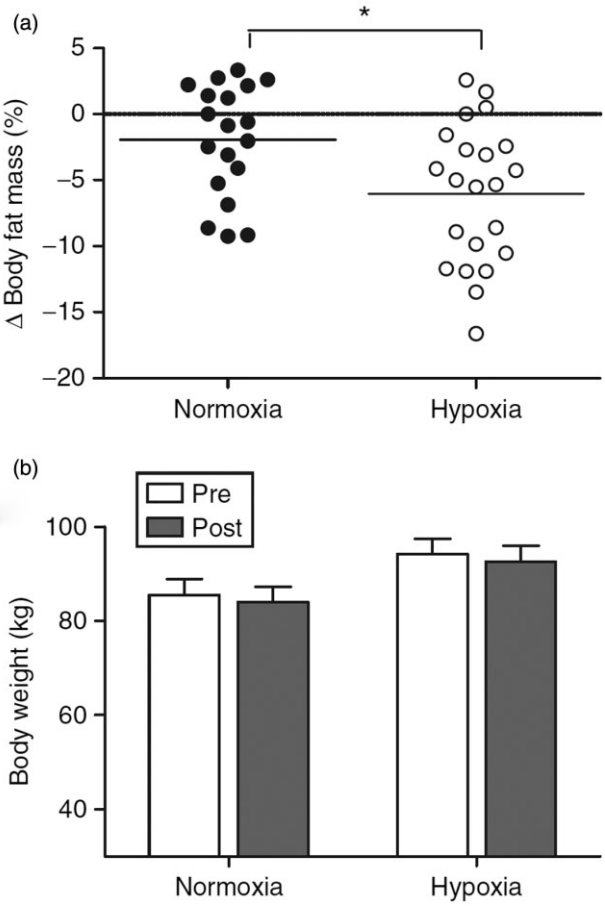

Figure 4 Body fat mass measured by bio-impedance analysis (panel a) and body mass (panel b) pre- and post-normoxic or hypoxic training in obese subjects. * significantly different between groups ($P < 0.05$) (from Wiesner *et al.* (119)).

insulin and EPO concentrations (117,118). One small trial in humans (12) compared in a blinded fashion the effect of low intensity endurance exercise for 90 min at 60% of the heart rate at maximum aerobic capacity, 3 d week^{-1} for 8 weeks, in either ambient 15% or 21% O_2 in two groups of 10 subjects with a BMI > 27. These preliminary data indicate that low intensity exercise training in normobaric hypoxia may lead to more weight loss than such training in normoxia (–1.14 vs. –0.03 kg). This difference in weight loss was however small (6 out of 10 subjects lost weight after hypoxic training vs. 4 out of 10 subjects after normoxic training) and no difference between training modalities was observed regarding BMI. In a single blind study with a similar population, Wiesner *et al.* (119) showed that training at 65% of heart rate at maximum aerobic capacity, for 60 min, 3 d week^{-1}, for 4 weeks, led to similar increases in maximal oxygen consumption and endurance but larger improvements in respiratory quotient and lactate at the anaerobic threshold as well as in body composition when performed in hypoxia (15% O_2) compared to normoxia (21% O_2) (Fig. 4). Interestingly, these results were obtained despite lower training workload in hypoxia, which may be beneficial for patients with orthopaedic comorbidities. The same group (13) also assigned 20 healthy men to a similar training programme in either 15 or 21% O_2 and found that body fat content, triglycerides, HOMA-Index, fasting insulin and area under the curve for insulin during an oral glucose tolerance test improved more when training in hypoxia compared to normoxia, despite the lower absolute exercise intensity (1.4 and 1.7 W kg^{-1} in hypoxia and normoxia, respectively). These results provide somewhat more credentials regarding the impact of hypoxic exposure in obese subjects compared to uncontrolled studies regarding altitude exposure (114,115). The limited data available so far, promising but to be confirmed in bigger trials, suggest that obese subjects might possibly profit of a '*sleep low and live (train) high*' paradigm as previously proposed for athletes (120) in terms of weight loss and/or cardiovascular and metabolic improvements. As mentioned earlier, there is a long tradition in the former Soviet Union countries of intermittent hypoxia training (11,121,122). Unfortunately, a lot of that tradition is hidden either because not published or published in Russian. Since hypoxia plays such an important role in the pathogenesis of obesity and related comorbidities, the weight of evidence in favour of therapeutic use of hypoxia for the treatment of obesity should be carefully evaluated. What sets such therapeutic intermittent hypoxic exposure apart from what OSA patients experience during sleep is the hypocapnia that accompanies the hypoxia while there are no apnoea periods, whereas in OSA there is hypercapnia during the hypoxia periods while breathing is obstructed. Little is yet known of what these differences imply. In any case, the current evidence base for the use of therapeutic daytime intermittent hypoxic exposure is still rather shallow. Since it has been shown that some modes of IH in healthy subjects may lead to increased

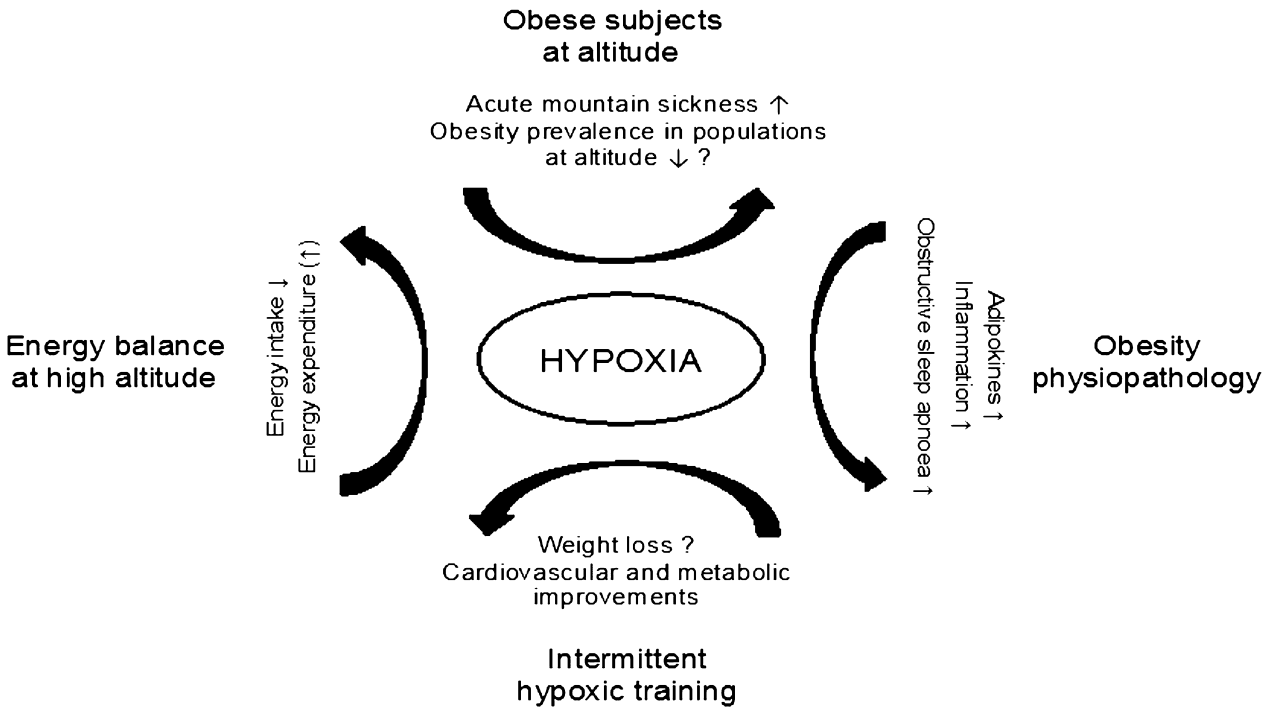

Figure 5 Overview of the relationships between hypoxia, energy balance and obesity.

blood pressure (123) further carefully controlled trials are necessary to confirm that hypoxic exposure in obese patients can be safe and without adverse effects, and to demonstrate that it would bring greater benefits than standard management strategies in normoxia.

Final remarks

High altitude exposure related weight loss would seem an interesting therapeutic adjunct for the treatment of obese subjects in order to improve their body composition. But high altitude exposure in such patients comes with increased risk due to their susceptibility to acute mountain sickness and their frequent comorbidities that can be potentially aggravated by altitude hypoxia. Hypoxia further seems an important factor of the pathogenesis of obesity-related comorbidities. On the other hand, hypoxia may be a two-sided sword since it can also induce positive adaptations (120). Hence, with optimal doses, intermittent hypoxia might become a potential adjunct tool for the prevention and treatment of metabolic and cardiovascular dysfunctions seen in obese patients (Fig. 5). Future research should confirm whether hypoxic training could be a new treatment strategy for weight loss and comorbidities in obese subjects and elucidate the underlying mechanisms and signalling pathways. The rather limited evidence available so far is promising but must to be confirmed in larger randomized controlled trials.

Conflict of interest statement

No conflict of interest was declared.

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