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Exercise and hypoxia: The role of the autonomic nervous system

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Abstract

The reduction in maximal oxygen consumption in hypoxia can be due to physiological factors, the relative importance of which depends on the degree of hypoxia: the reduction in inspired P_{O_2}, the impairment of lung gas exchange contributing to an exercise-induced decrease in arterial O_2 saturation, the reduction in maximal cardiac output and the limitation in tissue diffusion. This paper focuses on two aspects of this oxygen cascade. First, the decrease in heart rate at maximal exercise in prolonged exposure to hypoxia is discussed and the role of changes in the autonomous nervous system is emphasised. The desensitization of the beta-adrenergic pathway and the upregulation of the muscarinic pathway, both using G-protein systems, contribute to limit the myocardial O_2 consumption in face of reduced O_2 availability during maximal exercise in hypoxia. The changes in O_2 diffusion to the tissues are discussed in relation to the expression of hypoxia inducible factor (HIF-1α) and vascular endothelial growth factor (VEGF) and their possible changes induced by training and/or hypoxic exposure.

Keywords: Altitude; Exercise; Autonomic nervous system beta-adrenoceptors; Muscarinic receptors; Downregulation

1. Introduction

The capacity for exercise performance progressively decreases with increasing altitude (Fig. 1). This observation has been known for a long time and was particularly documented for the aerobic type of exercise involving an intense transport of oxygen from the ambient air to the mitochondria, site of oxygen utilization, along a series of steps known as the oxygen cascade. It has been debated by many authors the respective role of each of these steps in limiting the maximal rate of oxygen transport at exercise in hypoxia (Cerretelli, 1976; di Prampero and Ferretti, 1990; Gonzalez et al., 1993; Wagner, 1996; Richalet and Herry, 2006). The decrease in maximal oxygen consumption ($\dot{V}_{O_{2max}}$) is particularly dramatic at extreme altitudes, such as the summit of Mount Everest (8848 m) where almost only 25% of the sea level physical capacity remains available for the alpinist who climbs without supplementary oxygen. Since 1978 when Reinhold Messner and Peter Habeler reached, for the first time, the summit without oxygen, only 122 climbers (until 2005) realized the same achievement with success (Eguzkitza and Iturriza, 2006). It is important to note that the mortality among this category of himalayists is around 8%, suggesting that exercising with an arterial P_{O_2} of around 30 mmHg or less for hours causes severe damages and is a threat for life.

Living for a few days above 8000 m and even exercising at higher altitudes is possible only if time is given to the organism for acclimatisation to hypoxia. Bringing a non-acclimatised human being by helicopter to the top of Everest without supplementary oxygen leads to an inevitable death within minutes. One-month acclimatisation allows surviving and even exercising at the same altitude. All the processes that make possible this different response to the same constraint (adaptation process) is called "acclimatisation", the term "adaptation" being generally limited to the permanent, especially genetic, changes. These processes are accompanied by a decrease in the overall energy cost of the responses to the hypoxic stress (Richalet, 2007).

A complex machinery of responses is triggered when an aerobic organism is exposed to hypoxia, involving all cells through the activation of genes presenting a hypoxia responsive element (HRE). Many factors respond to hypoxia, such as hypoxia inducible factor (HIF-1α), vascular endothelial growth factor (VEGF), erythropoietin (EPO), etc. These factors are responsible for initiating physiological processes which, for some of them, will reduce the level of tissue hypoxia (Richalet, 1997). One of the principal response systems to hypoxia is triggered by the stimulation of the peripheral chemoreceptors and involves,

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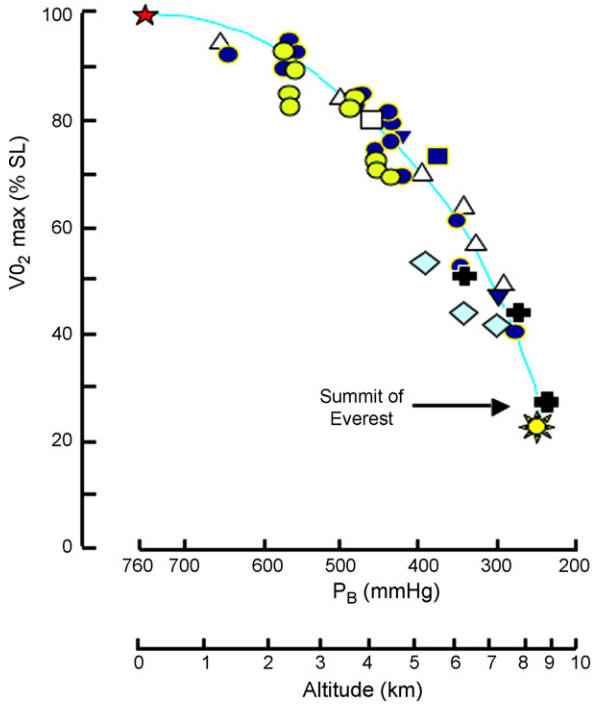

Fig. 1. Decrease in maximal oxygen consumption with increasing altitude. Symbols correspond to mean values obtained in various studies. Adapted from Cerretelli (1992) and Richalet and Herry (2006).

from one side the activation of ventilatory control centres, from the other side the activation of the cardiovascular control centres. The stimulation of the adrenergic nervous system is responsible for the acute cardiovascular response to hypoxia, i.e. tachycardia and increase in cardiac output that will try to compensate the acute decrease in blood oxygen content. As one of the most powerful response to the hypoxic stress, the sympathetic system and its counterpart, the parasympathetic system will play a crucial role in the adaptation to acute and chronic hypoxia during exercise. This paper will try to review the most important features concerning the role of the autonomic nervous system in the adaptation of the cardiovascular system during exercise in hypoxia. It will particularly focus on humans and hypoxia-sensitive animal species.

2. Oxygen delivery at exercise in acute and chronic hypoxia

The reduction in $\dot{V}_{O_{2max}}$ in hypoxia is due to four main factors, the relative importance of which depends on the degree of hypoxia: the reduction in inspired P_{O_2}, the impairment of gas exchange (DLO_2) inducing an exercise-induced arterial desaturation, the reduction in maximal cardiac output and the limitation in tissue diffusion. The mechanism of arterial desaturation during maximal exercise was shown to be directly due to the decrease in Pa_{O_2} in humans, while in rats where Pa_{O_2} is higher, it seems that the desaturation could be due to a large Bohr effect in this species (Gonzalez et al., 1991).

Acclimatisation to hypoxia induces polycythemia secondary to erythropoietin (Epo) release by the kidney to increase arterial oxygen content (Richalet et al., 1994). However, despite a marked increase in O_2 carrying capacity, $\dot{V}_{O_{2max}}$ changes little after acclimatisation (Bender et al., 1988; Cerretelli, 1976). This lack of effect of acclimatisation on $\dot{V}_{O_{2max}}$ is partly attributed to a decrease in maximal cardiac output ($\dot{Q}_{max}$) observed in both rats and humans which offsets the increase in arterial blood O_2 content (Favret et al., 2001; Grover et al., 1986). Supporting $\dot{Q}_{max}$ as a factor limiting $\dot{V}_{O_{2max}}$ is the observation that increasing maximal heart rate (HR_{max}) and $\dot{Q}_{max}$ by cardiac pacing increases $\dot{V}_{O_{2max}}$ of rats acclimitised to prolonged hypoxia (Gonzalez et al., 1998).

The reduction in $\dot{Q}_{max}$ in prolonged hypoxia has been attributed to several factors (Wagner, 2000): (1) reduction in blood volume and cardiac filling, (2) increased blood viscosity and vascular resistance, (3) alterations in the control by the autonomous nervous system, (4) passive reduction due to a tight coupling between muscle O_2 consumption (which is reduced for metabolic causes) and cardiac output. We will particularly focus in this paper on the third hypothesis which seems to be based on the greatest experimental evidence. Since Christensen and Forbes (1937), the reduction in HR_{max} at high altitude has been observed by many authors (review in Richalet, 1990; Lundby et al., 2001). Above 4000 m, the reduction in maximal cardiac output and heart rate becomes an important limiting factor. However, the importance of this reduction has been debated since the advantage of rising cardiac output to increase O_2 transport to the periphery can be offset by the disadvantage of increasing diffusion impairment in the lungs (Wagner, 2000). The mechanisms of reduction of HR_{max} are to be looked for in the control of the cardiovascular system by the autonomous nervous system. We will try to review the present knowledge about this important process of adaptation to hypoxia during exercise.

The activation of the adrenergic system in acute hypoxia has been evidenced by direct and indirect observations. Plasma and urine norepinephrine concentrations have been found elevated in most studies performed in acute and chronic hypoxia, at rest or at a given absolute level of exercise (Richalet, 1990; Mazzeo et al., 1991). The direct measurement of the activity of adrenergic fibres has also evidenced an increase in sympathetic activity in hypoxia (Seals et al., 1991). The hypoxia induced tachycardia is responsible for an increase in cardiac output in hypoxia, for a given level of O_2 consumption (Gonzalez et al., 1998). The decrease in arterial O_2 content in acute hypoxia cannot be fully compensated by an equivalent decrease in O_2 venous content in the working muscles, so that the arterio-venous O_2 difference decreases and cardiac output increases.

In humans as well as in other mammals, prolonged hypoxia tends to reduce resting and exercise heart rate while circulating catecholamines remain elevated (Antezana et al., 1994). These results can suggest either a decrease in the responsiveness of the adrenergic system to stimulation or an increase in parasympathetic activity (Hartley et al., 1974; Boushel et al., 2001; Savard et al., 1995). Both hypotheses can be validated by some experimental evidence.

The responsiveness of the adrenergic system to endogenous (exercise) or exogenous (isoproterenol infusion) stimulation is decreased in prolonged hypoxia (Maher et al., 1978; Richalet

et al., 1988a,b, 1989). For example, for a given increase in norepinephrine plasma concentration from rest to exercise, the corresponding increase in heart rate is lower in prolonged hypoxia than in normoxia (Richalet et al., 1988a). The infusion of increasing doses of isoproterenol leads to a lower increase in heart rate in prolonged hypoxia versus normoxia in humans (Richalet et al., 1988b, 1989) or in dogs (Maher et al., 1978). This blunted response to adrenergic activation is partly rapidly reversible with re-oxygenation (Richalet et al., 1989).

This hypoxia induced blunted responsiveness of the adrenergic system has been explored through the study of signal transduction in the main receptor systems controlling cardiac chronotropic function: β-adrenergic (β-AR), muscarinic (M-Ach-R) and adenosinergic receptors. Acute hypoxia (1–5 days at 4559 m) has been found to reduce HR_{max} and this reduction was fully reversible with O_2 inhalation, which suggests an uncoupling of β-AR, as a result of phosphorylation of G-protein or second messenger, rather than a downregulation of the receptor (Lundby et al., 2001). Chronic hypoxia leads to a down regulation of β-AR in the rat myocardium (Voelkel et al., 1981; Kacimi et al., 1992) and in human lymphocytes (Antezana et al., 1994). This decrease is associated with a decrease in adenylate cyclase activity in rats (Kacimi et al., 1992; Mardon et al., 1998; Hrbasova et al., 2002; Pei et al., 2000) and in guinea pigs (León-Velarde et al., 1996). The effects of hypoxia on the adrenergic pathway could be mediated by the desensitising effect of permanently increased catecholamine levels or to a direct effect of hypoxia on one or several elements of the transduction pathway. To test this hypothesis, chronically hypoxic rats were compared to rats exposed to prolonged norepinephrine infusion (León-Velarde et al., 2001). There were some clear differences between the two models, especially at the level of Gi inhibitory protein that was more activated in hypoxic rats than in rats exposed to norepinephrine. The changes are also very much chamber dependent, since in rats exposed to chronic hypoxia, the right ventricle is hypertrophied and in the norepinephrine stimulated group the left ventricle is hypertrophied (León-Velarde et al., 2001). Several studies have also observed that chronic exposure to hypoxia led to an increase in the density of myocardial M-Ach-R (Favret et al., 2001; Kacimi et al., 1993; Wolfe and Voelkel, 1983). These results are consistent with the hypothesis that myocardial β-adrenergic receptors as well as muscarinic receptors are involved in the reduction of maximal heart rate after acclimatisation to hypoxia (Favret et al., 2001). Favret et al. (2001) provided clues of the possible role of myocardial β-AR and M-Ach-R on $\dot{Q}_{max}$ by studying the time course of acclimatisation. They showed a strong correlation between ventricular β-AR density (Fig. 2A) as well as M-Ach-R density (Fig. 2B) and HR_{max}. These results suggest that β-AR downregulation and M-Ach-R upregulation could be considered as a possible mechanism leading to the reduction of HR_{max} and $\dot{Q}_{max}$. Boushel et al. (2001) have shown, by parasympathetic blockade using glycopyrrolate, that the parasympathetic nervous system was involved in the decrease in HR_{max} in human acclimatised to 9 weeks at 5260 m. In subjects acclimatized for 2 weeks at a much lower altitude (3800 m), glycopyrrolate also increased HR_{max} but failed to significantly increase maximal

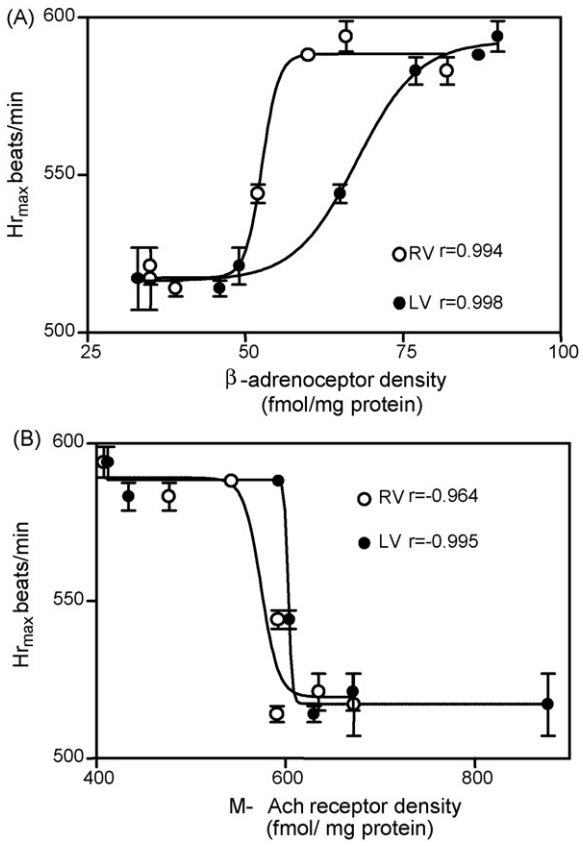

Fig. 2. HR_{max} as a function of β-AR and muscarinic receptor density. From Favret et al. (2001).

cardiac output (Bogaard et al., 2002). However, in rats acclimatised for 3 weeks at 5500 m, Clancy et al. (1997) did not observe that the M-Ach-R were responsible for the low HR_{max}. Prolonged exposure to severe hypoxia (3 weeks at 6542 m) leads to a permanent increase in adrenergic activity (although plasma norepinephrine decreases from the first to the third week of exposure), a decrease in the density of β-AR in circulating lymphocytes and in the heart rate response to isoproterenol infusion (Antezana et al., 1994). The desensitization of the β-adrenergic pathway is not only linked to the decrease in the β-AR density but also to an alteration of the Gs protein coupling to adenylate cyclase (Kacimi et al., 1995). The impaired function of Gs could be due to a reduction in the biologically active form Gsα-small and/or an increase in the biologically inactive form Gsα-large of the Gs protein (Pei et al., 2000). Moreover, the bioactivity of the membrane-bound Gsα would be reduced (Hrbasova et al., 2002). The stimulation of adenosinergic receptors, by activating the inhibitory Gi protein can also reduce the adenylate cyclase activity, although these receptors are also downregulated in hypoxia (Kacimi et al., 1995). The Gi protein has been found increased in the heart of rats exposed to 5 days of hypoxia (Mardon et al., 1998). An impairment of norepinephrine intravesicular uptake in hypoxia could also contribute to increase the concentration of norepinephrine in the synaptic space and contribute to the desensitization of the adrenergic pathway (Richalet et al., 1990; Mardon et al., 1998). Opioid receptors can also be involved since a cross-talk exists between these receptors and

β-AR: the pertussis toxin-sensitive G-protein of the opioid pathway inhibits the Gs protein of the adrenergic pathway (Wong and Shan, 2001). The release of dynorphins from the heart in hypoxia can activate the kappa opioid receptors and blunt the adrenergic pathway, therefore protecting the heart from too high energy consumption (Wenzlaff et al., 1998). These adaptations of the autonomic control of the heart in hypoxia seem well established even in species genetically adapted to high altitude, such as the guinea-pig living on the Altiplano (León-Velarde et al., 1996).

Altogether, it appears that many observations are in favour of an important role of the changes in the autonomic nervous system in mammals acclimatised to hypoxia, as limiting $\dot{V}_{O_{2max}}$ despite increased O_2 carrying capacity.

In a model of oxygen transport in the myocardium, it was clearly shown that the maintenance of a normal myocardial tissue P_{O_2} at maximal exercise in hypoxia was possible at the only condition that the myocardial energy expenditure decreases, that is to say that maximal heart rate decreases (Richalet, 1990). Therefore, the currently observed decrease in HR_{max} in chronic hypoxia would be a homeostatic mechanism contributing to the maintenance of myocardium tissue oxygenation, despite a decrease in oxygen supply (Fig. 3). By reducing maximal O_2 transport, the decrease in HR_{max} can be considered as a limiting factor of performance at high altitude. However, this mechanism is protective for the heart, a vital organ that is also demanding for a high O_2 supply at exercise. The coronary flow reserve has been shown to be limited to 33% above what is prevailing during maximal exercise at sea level (Kaijser et al., 1990). Therefore, the compensation of decreased arterial O_2 content by increasing coronary blood flow is not possible above a certain altitude and the only option to preserve cardiac integrity is to decrease myocardial O_2 demand and therefore maximal heart rate. It is important to note that there is no need to involve the brain and a hypothetic central governor to explain the reduction

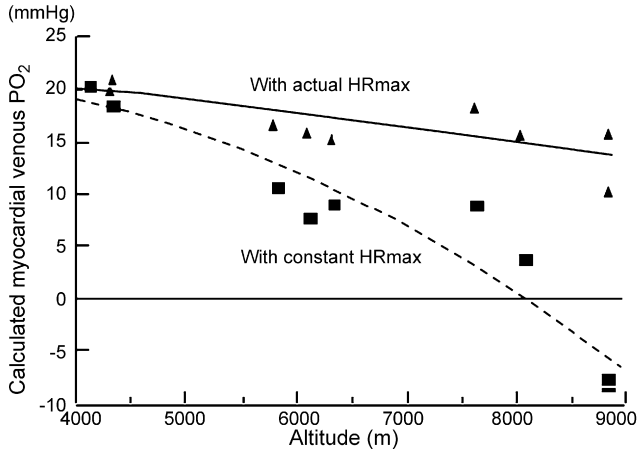

Fig. 3. Variations of calculated venous myocardial P_{O_2} as a function of altitude, at maximal exercise. Values were calculated using data obtained at maximal exercise from various studies in the literature. When HR_{max} is entered in the equation for the computation of P_{O_2} as actual HR_{max} (which decreases with altitude; see Fig. 4), myocardial venous P_{O_2} is almost kept constant whatever the altitude. When an invariable constant value (sea level value) of HR_{max} is used, predicted P_{O_2} is negative above 8000 m. For details and references, see Richalet (1990).

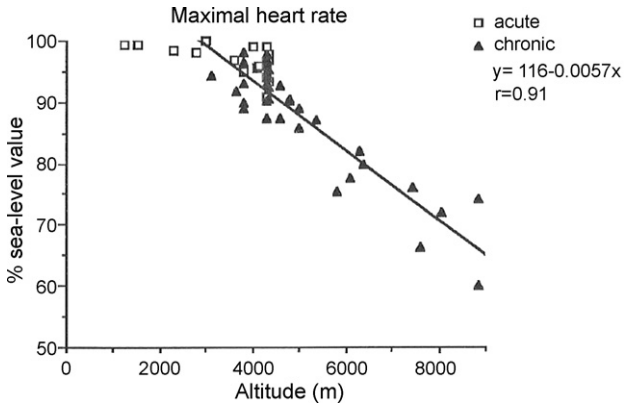

Fig. 4. Maximal heart rate (HR_{max}) as a function of altitude in acute and chronic hypoxia. From Richalet (1990).

in $\dot{V}_{O_{2max}}$ and HR_{max} in hypoxia (Noakes, 2000). This theory supposes that a tissue sensor alerts the brain and reduces heart rate when the availability of O_2 is low. No such mechanism has ever been evidenced, except in very severe cerebral ischemia, which is not the case at altitudes such as 4000 m where the decrease in HR_{max} is already significant (Fig. 4). On the contrary, hypoxia, via the chemoreceptors and the medullar control centres, always induces an activation of the adrenergic system and therefore an increase in heart rate. The downregulation of the β-adrenoceptors and upregulation of the muscarinic receptors within the myocardium are sufficient to explain the decrease in HR_{max} and are purely local homeostatic mechanisms that protect the myocardium against a too high energy expenditure. It is important to note that all these changes in cardiac chronotropic function are not associated with alterations in the inotropic function. Stroke volume and myocardial contractility, explored by echocardiography up to the simulated altitude of 8848 m are not diminished, at least at rest (Boussuges et al., 2000).

Acclimatisation to hypoxia can also induce beneficial changes at the tissue level improving O_2 flux from the capillary to the mitochondria but these data are still discussed following the model used and the time and the altitude of exposure (Mathieu-Costello, 2001). Exposure to hypoxia increases the expression of hypoxia inducible factor (HIF-1), a transcriptional factor that activates many genes with HRE, such as the vascular endothelial growth factor (VEGF) (LaManna et al., 2004). The alpha component of this dimeric factor accumulates immediately due to hypoxic inhibition of prolyl hydroxylase, which is responsible for the continuous degradation of HIF-1α under normoxic conditions. Deveci et al. (2002) have demonstrated that 6 weeks of exposure to 4200 m resulted in a marked increase in the capillary/fibre ratio in the diaphragm and in the soleus which could increase surface area and improves O_2 transfer from the capillary bed to the skeletal muscle. However, Olfert et al. (2001a) have observed that chronic hypoxia alone did not result in an increase in VEGF mRNA and in capillary/fibre ratio in rats acclimatised at 4200 m for 8 weeks. These results agree with the fact that acclimatisation did not enhance oxygen tissue diffusion in rats exposed 10 days at 5500 m (Favret et al., 2006). Similarly, in sea level human natives acclimatized for 8 weeks

at 4100 m, no change was observed in capillary density or in mRNA expression of VEGF of HIF-1α (Lundby et al., 2004). At extreme altitude, skeletal muscle mass decreases resulting in an increase in the capillary/fibre ratio without angiogenesis. The result of this change is a greater O_2 flux to mitochondria caused by the reduction of diffusion distance and an indirect increase in surface area (Hoppeler and Vogt, 2001).

In summary, while chronic hypoxia could clearly induce angiogenesis through HIF and VEGF pathways in the brain (LaManna et al., 2004), the effect of chronic hypoxia on the capillary/fibre ratio and subsequently on O_2 transfer to the skeletal muscle is still debated.

3. Effects of training status on the response to exercise in hypoxia

The well-known fall in $\dot{V}_{O_{2max}}$ is also described in endurance trained mammals (rats and human). It has been observed that the fall in $\dot{V}_{O_{2max}}$ was greater in endurance trained rats compared to sedentary (Favret et al., 2003). The arterial desaturation was larger in trained animals despite an increase in arterial P_{O_2} (Favret et al., 2003, 2006) which could be due a better efficacy of pulmonary gas exchange. Indeed, oxygen lung diffusion capacity (DLO_2) was increased in trained rats. As previously observed the arterial desaturation could be attributed to the more severe acidosis developed in trained rats during maximal exercise resulting in a greater Bohr effect. A larger decrease in $\dot{V}_{O_{2max}}$ in trained versus untrained individuals has also been demonstrated in humans (Martin and O'Kroy, 1993; Woorons et al., 2005; Mollard et al., 2007). The difference has been mainly attributed to a larger arterial desaturation at exercise in hypoxia, both because of a higher cardiac output (and shorter pulmonary transit time) and a greater O_2 extraction by the muscles in trained subjects, leading to a lower P_{O_2} in the mixed venous blood reaching the lungs.

The "living high-training low" method was first described by Levine et al. (1991) to improve $\dot{V}_{O_{2max}}$ at sea level. Briefly, the method consists in living at high altitude to enhance arterial O_2 content following increased eythropoiesis and training at low altitude to keep a high intensity training. In rats, Hendersonn et al. (2001) have used a different model called "living high-training high" which was compared to a "living low-training low" model. Rats were trained and exposed continuously either to normoxia or to 2500 m. This study showed that exercise training induces an increase in $\dot{V}_{O_{2max}}$ in normoxia without effects in hypoxia. The lack of change in $\dot{V}_{O_{2max}}$ in acclimatised and trained rats was partly attributed to the hemoglobin concentration which was unchanged in these rats. It appeared then that 10 weeks of exposure to 2500 m was not enough to induce polycythemia.

Favret et al. (2003) used a model closed to "living high-training low" to prove that previous exercise training could influence the autonomic nervous system and therefore improve $\dot{V}_{O_{2max}}$ after acclimatisation to hypoxia. Indeed, it has been previously shown that endurance exercise training resulted in a decrease in sympathetic activity (Mazzeo and Grantham, 1989) which could offset the drive due to hypoxic exposure. This study showed that exercise training attenuated the downregulation of β-adrenoceptors observed during hypoxia and moderated the reduction in HR_{max} following acclimatisation and therefore improved $\dot{V}_{O_{2max}}$ (Fig. 5A). The results have shown that $\dot{V}_{O_{2max}}$, in normoxia and in hypoxia, were increased in endurance trained rats but to a larger extent in acclimatised rats (Favret et al., 2003). These results were linked to an increase in arterial O_2 content due to acclimatisation and a lower reduction in HR_{max} in acclimitised rats allowing an increase in O_2 delivery. Moreover, the upregulation of M-Ach receptors observed in acclimitised rats was prevented by endurance training which could also participate to a lower reduction of HR_{max} (Fig. 5B).

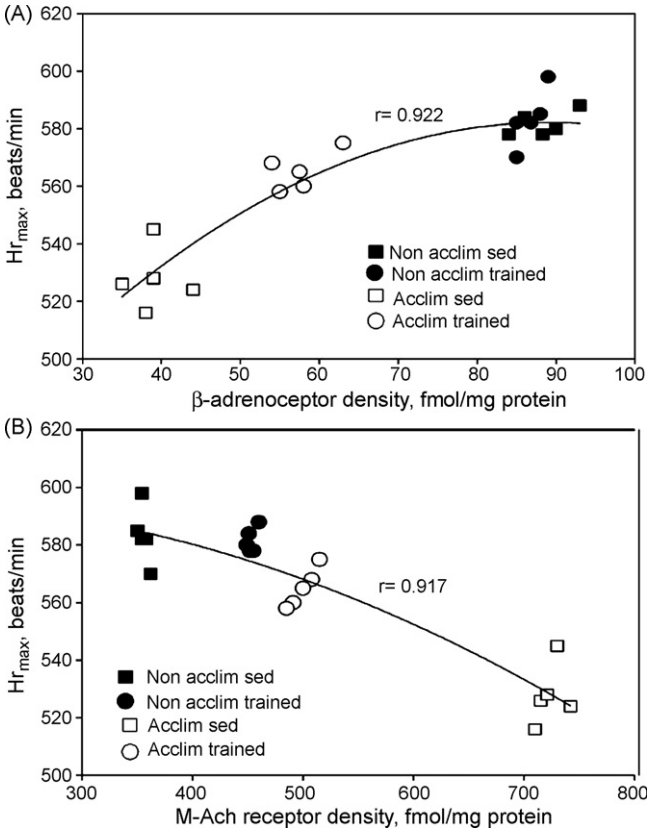

Fig. 5. HR_{max} as a function of β-AR and muscarinic receptor density in trained and sedentary rats, acclimatized or not to hypoxia. From Favret et al. (2003).

In conclusion, the "living high-training low" method could improve $\dot{V}_{O_{2max}}$ more than "living low-training low" but the altitude used to induce polycythemia should be important in rats. Moreover, previous endurance exercise training seemed to be a beneficial strategy to offset the decrease in HR_{max} in acclimitised rats and therefore maintain maximal cardiac output which represents the major limiting factor of $\dot{V}_{O_{2max}}$ in hypoxia in acclimatised rats.

At the tissue level, numerous studies have demonstrated the effect of hypoxia on angiogenesis, oxygen diffusion capacity and skeletal muscle aerobic capacity following endurance exercise training in hypoxia or normoxia (Abdelmalki et al., 1996; Hoppeler and Vogt, 2001; Olfert et al., 2001b).

We have previously observed that acclimatisation to high altitude (5500 m) did not improve tissue oxygen diffusion more in trained rats when maximal exercise was performed in nor-

moxia and in hypoxia (Favret et al., 2003). However, when exercise training was performed at high altitude (4200 m) in rats, Olfert et al. (2001b) have shown that the capillary/fibre ratio was increased, in agreement with previous works (Bigard et al., 1991). In this elegant study, Olfert et al. (2001b) observed a decrease in VEGF mRNA after 8 weeks of hypoxic exposure in both trained and untrained rats. Depending on the altitude used and the model of exercise training (in hypoxia or in normoxia), acclimatisation to hypoxia could lead or not to an increase in capillary/fibre ratio improving tissue O_2 diffusion. Bigard et al., 1991 reported that, in rats, exercise training in hypoxia enhanced the activity of enzymes involved in the citric acid cycle and the β-oxidation of fatty acids in the extensor digitorum longus and in the plantaris while no change was observed in the soleus. Favret et al. (2003) have shown that acclimatisation to hypoxia (10 days at 5500 m) reduced the aerobic capacity of the rat skeletal muscle (gastrocnenius) through a fall in citrate synthase activity.

4. Perspectives

The precise role of each factor participating in the transport of oxygen at exercise in hypoxia remains to be established. This is a complex system where, while the influence of each factor, isolated from the rest of the system, is quite easy to predict, its precise role, when the whole system is closed and interacting, is difficult to assess without the help of mathematical models (Wagner, 1996). Among factors affecting O_2 delivery at high altitude, polycythemia is a key factor of acclimatisation. However, its role has been challenged in some studies where hemodilution in acclimatized lowlanders failed to reduce $\dot{V}_{O_{2max}}$ (Calbet et al., 2004). Recently, in a model of transgenic EpoTag^h mice underexpressing Epo, demonstrated that chronic anemic mice could acclimatise to hypoxia partly through an increase in ventilation and ventilatory response to hypoxia (Macarlupú et al., 2006). Therefore, it seems that increased erythropoieis is not required for a normal metabolic activity at high altitude, at least in resting conditions.

The role of transgenic models under or overexpressing genes involved in the oxygen transport system can be of valuable interest for future research in this domain. For example, a model of mice overexpressing β-adrenergic receptors (Cerretelli, 1992; Gaussin et al., 2003) would be of great interest to explore the physiological significance of their hypoxia-induced down-regulation and their contribution to limit HR_{max} and decrease myocardial energy expenditure in chronic hypoxia.

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