The Journal of Experimental Biology 201, 1243–1254 (1998)
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JEB1359

MECHANISM AND EVOLUTION OF HYPOXIA-TOLERANCE IN HUMANS

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Accepted 15 October 1997; published on WWW 24 March 1998

Summary

To physiologists, the term 'adaptation' usually refers to any trait that is considered advantageous; evolutionary biologists require a more rigorous definition (restricting it to traits arising and maintained under selection). By their definition, many physiological traits may merely reflect inheritance passed on through lineage. In considering the evolution of tolerance to reduced oxygen availability, we examined the issue (of true adaptations *versus* simple inheritance) in pinnipeds (the two dominant groups, phocids and otariids, with varying diving capacities) and in human lineages exposed for varying generational periods to hypobaric hypoxia. Basic principles of the evolution of complex physiological systems first emerged from an analysis of the diving response. We then analyzed human responses to hypobaric hypoxia in three different lineages: lowlanders, Andean natives (Quechuas) and Himalayan natives (Sherpas). As in the pinniped example, we found 'conservative' and 'adaptable' physiological characters involved in human responses to hypoxia. Conservative characters are clearly dominant and are too numerous to outline in detail; three examples are haemoglobin oxygen-affinities, the organization of muscle into different fibre types and the brain's almost exclusive preference for glucose as a fuel. Most notably, we also found evidence for 'adaptable' characters at all levels of organization examined. At the whole-body level in Quechuas and Sherpas, we found (i) that maximum aerobic and anaerobic exercise capacities were down-regulated, (ii) that the acute effect of hypoxia (making up the energy deficit due to oxygen lack; i.e. the Pasteur effect) expected from lowlanders was blunted, and (iii) that acclimation effects were also attenuated. The biochemical behaviour of skeletal muscles was consistent with lowered reliance on glycolytic contributions to energy supply, thus improving the yield of ATP per mole of carbon fuel utilized. Heart adaptations also seemed to rely upon stoichiometric efficiency adjustments, improving the yield of ATP per mole of oxygen consumed (by using glucose in preference to fatty acids). Most of the biochemical and physiological adaptations we noted (both as acute and as acclimation responses) were similar in Sherpas and Quechuas. These two lineages have not shared a common ancestor for approximately one-third of the history of our species, so it is possible that their similar physiological traits arose independently as hypoxia defence adaptations in two different times and places in our history. As in the evolution of exquisite capacities for management of oxygen down to vanishingly low levels in diving animals, the evolution of human hypoxia-tolerance can be described in terms of how two (conservative *versus* adaptable) categories of physiological characters are assembled in different human lineages and how the assembly changes through generational time. More recent evidence indicating that our species evolved under 'colder, drier and higher' conditions suggests that these adaptations may represent the 'ancestral' physiological condition for humans.

Key words: hypoxia-tolerance, endurance performance, high altitude, Quechua, Sherpa, evolutionary physiology.

Introduction

The science of comparative and integrative physiology stems from two main intellectual roots – mechanism and evolution. Mechanistic comparative physiology, historically the first and traditionally the dominant of these two approaches, uses organisms as an experimental parameter *per se*, taking advantage of lineage-specific characteristics to help determine how fundamental biological processes work. The dominance of this approach was challenged about a decade ago by a group who argued that it is 'no longer a new or even young field', that 'it has lost the shine of first discovery' and that it is at risk of an extinction event analogous to the extinction of comparative anatomy in the mid-twentieth century (Bennett, 1987). Equally gloomy was the assertion that the discovery of patterns of physiological adaptation to the environment, the 'historic mission' of our discipline, occurs at an ever decreasing rate; in terms of providing new insights and new concepts, the field (as for physics in the late 1900s) is now approaching the point of diminishing returns (Feder, 1987). This 'sobering and

unexciting experience for everyone in the field' (Bennett, 1987) is not restricted to comparative physiology; our mainstream (mammalian and medical physiology) colleagues have been undergoing similar soul searching, which was initially rather despondent, but has recently taken a more positive tone (see APS LRPC Report, 1990, 1996).

Evolutionary physiology, described by Feder (1987) as our 'new mission', is the acknowledged second major root from which the field grows, and in earlier manifestations it aimed to sort out major evolutionary pathways of physiological systems. The tips of phylogenetic trees were examined in enormous detail; then the branches were sketched in, forming hypothetical (some would even say, imaginary) evolutionary pathways. Today, modern biologists have devised much more rigorous methods for working out evolutionary details in the phylogenetic histories of physiological systems. Flushed with success, some workers in this field would be happy to see evolutionary physiology replace mechanistic physiology as the only acceptable research alternative. Elsewhere (Mangum and Hochachka, 1998), we have argued that fusing these two main streams of current physiology seems to present perhaps the most vigorous trajectory for our discipline into the next century. To illustrate this position, we here attempt to combine mechanistic and evolutionary approaches to human hypoxia-tolerance.

Background

The starting point for our thinking on this problem was recent studies on the origins and evolution of hominids, which implied that the human species arose in environments that were becoming drier and higher; that is, conditions under which endurance performance capacities and hypoxia-tolerance would have been favoured (Vrba, 1994). This aroused our interest since biomedical researchers have long known that there are quite a few mechanistic similarities in human physiology between adaptations for endurance performance and for hypoxia-tolerance (Brooks *et al.* 1996; Levine and Stray-Gunderson, 1992, 1997; Terrados, 1992; Green, 1992). How physiological systems for hypoxia-tolerance or endurance performance might have evolved within our phylogeny was not investigated earlier because there were few, if any, guidelines for tracing the evolutionary pathways of complex physiological systems in humans or in animals. In our case, initial guidelines arose from recent quantitative analyses of the variability of the diving response in pinnipeds. These studies (Hochachka and Mottishaw, 1998; P. D. Mottishaw, S. J. Thornton and P. W. Hochachka, in preparation) led to three principles of evolution of the diving response which we found useful as framework for probing the evolution of complex physiological systems. (i) Some physiological/biochemical characters considered necessary in diving animals are conserved in all pinnipeds; these traits (including diving apnoea, bradycardia, tissue hypoperfusion and hypometabolism of hypoperfused tissues) probably arose in response to factors other than – or in addition to – diving requirements and presumably were and are maintained largely by negative or balancing selection (any mutations affecting them not surviving). At this stage in our understanding of diving physiology and biochemistry, we are unable to detect any correlation between these characters and diving capacity, even though they are clearly used during diving and are so important that diving bradycardia is often referred to in the literature as the 'master switch of life'. (ii) A few other diving 'characters' or traits are more malleable and are clearly correlated with long-duration diving and prolonged foraging at sea. These characters are more lineage-specific, and include spleen mass, blood volume and red blood cell (RBC) mass. The larger these are, the greater the diving capacity (defined as diving duration). Since the relationships between diving capacity and any of these traits are evident even when corrected for body mass, it is reasonable to conclude that these three traits – large spleens, large blood volume and large RBC mass – extend diving duration, probably through effects on O_2 storage and O_2 management during diving. That is, in contrast to conserved traits such as bradycardia, these kinds of characters have evolved presumably by positive selection to enable prolonged dive times. (iii) The evolutionary physiology of the diving response can thus be described in terms of the degree of development of adaptable *versus* conservative categories of diving characters; i.e. in terms of how these patterns change through time and how the patterns are lineage-specific.

The relationship between time and adaptation

Stimulated by these studies, we then turned our attention to human responses to hypobaric hypoxia based on studies (Allen *et al.* 1997; Hochachka *et al.* 1991, 1992, 1995, 1996*b*,*c*, 1997; Holden *et al.* 1995; Matheson *et al.* 1991) with several different low- and high-altitude human lineages. To appreciate our approach, it is important to explain that the strategies utilized for dealing effectively with environmental or other selectively significant parameters depend upon the time available for the response. Traditionally, the time-line for response is divided into three categories: acute, acclimatory and genetic or phylogenetic (Hochachka and Somero, 1984). The formal relationship between these three time-lines of responses can be described as follows. First, initiating the whole cascade are sensing mechanisms, which tell the organism when the problem arises and perhaps how serious it is. Second, this information must be transduced at various levels of organization into appropriate functional responses. Third, a specific set of signal transduction pathways is involved in the acute responses to the stress. Fourth, either the same or different sets of signal transduction pathways may be utilized to orchestrate more complex acclimatory responses. Fifth, all of the above – the sensing step, the signal transduction pathways, the acute response and the acclimatory responses – may change gradually through phylogenetic time.

Acute and acclimation responses in lowland lineages

In acute high-altitude exposure, current evidence from

diverse studies of both human and animal models indicates that hypoxia defences are initiated by several oxygen-sensing, signal transduction pathways. For convenience, we can summarize these as five general hypoxia response systems (Figs 1–5): (i) carotid body O_2 sensors (Acker and Xue, 1995; Lahiri, 1996) initiate the hypoxic ventilatory response (HVR) which, despite an alkalosis risk (Samaja *et al.* 1997), serves to compensate for the acute oxygen shortage (see Fig. 1); (ii) pulmonary vasculature O_2 sensors (Youngson *et al.* 1993; Weir and Archer, 1995) initiate regulation of the hypoxic pulmonary vasoconstrictor response (HPVR) and hence adjustments in lung perfusion and in ventilation–perfusion matching (Heath and Williams, 1991) (see Fig. 2); (iii) O_2 sensors in the vasculature of other tissues activate expression of vascular endothelial growth factor 1 (VEGF1) (Forsythe *et al.* 1996) with its receptor (Detmar *et al.* 1996) and thus promote angiogenesis, especially in the heart (Ogita *et al.* 1995; Ladoux and Felin, 1993) and probably the brain (Harik *et al.* 1996) (see Fig. 3); (iv) O_2 sensors in the kidney and liver activate the expression of erythropoietin (EPO) and so begin the process of up-regulating red blood cell (RBC) mass (Goldberg *et al.* 1998; Maxwell *et al.* 1993; Wang *et al.* 1995; Wenger and Gassmann, 1997) (see Fig. 4); and (v) tissue-specific O_2-sensing and signal transduction pathways lead to metabolic reorganization (Hochachka *et al.* 1991, 1995, 1996*a*,*b*,*c*), presumably by altering the rates of expression of hypoxia-sensitive genes for metabolic enzymes and metabolite transporters (Bunn and Poyton, 1996; Hochachka *et al.* 1996*a*; Wenger and Gassmann, 1997) (see Fig. 5).

Even though no sharp line separates the acute and acclimatory phases of hypoxia-exposure, it is clear that most hypoxia response systems do not have time to reach completion during acute hypoxia. Thus, despite these adjustments, the debilitating effects of acute hypoxia-exposure are easily measurable and can be illustrated by considering an exercise protocol. On exposure to acute hypoxia (equivalent to approximately 4200 m in altitude), there is a relatively large (20–35 %) decline in the maximal rate of oxygen uptake ($\dot{V}_{O_2max}$) in lowlanders (Martin and O'Kroy, 1992). Furthermore, metabolic attempts to make up the energy deficit due to O_2 lack are expressed as large increases in lactate accumulation in the blood during exercise (see Hochachka *et al.* 1991, for representative data).

With continued exposure of lowland lineages to hypoxia, acclimation processes (i) increase the hypoxia-sensitivity of the HVR (at the biochemical level, this may require increasing the O_2 affinity of the O_2 sensor; Hochachka, 1994; Bunn and Poyton, 1996) and, for a given hypoxic stimulus, the ventilatory response is exaggerated (Lahiri, 1996). Acclimation also (ii) extends the HPVR, sometimes causing

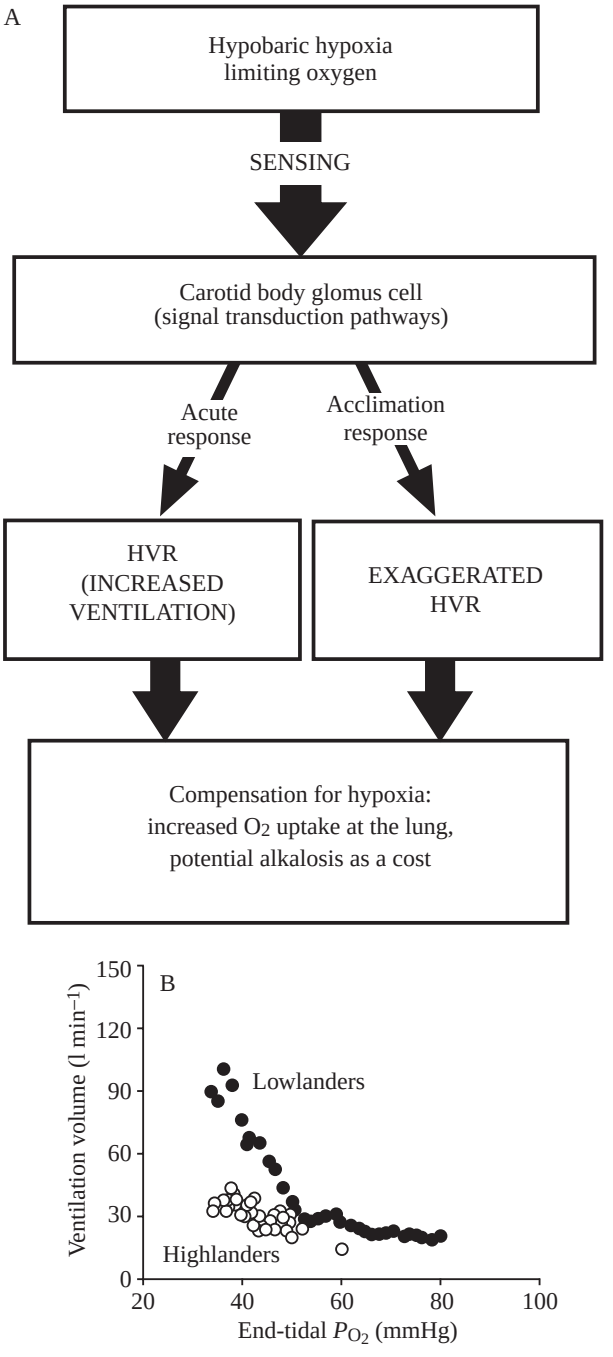


Fig. 1. (A) Diagrammatic summary of the formally defined relationships between time and physiological responses (in this case, the hypoxic ventilatory response or HVR) to environmental factors such as hypoxia. Acute responses are those that occur essentially instantaneously with environmental change; adjustments requiring some fraction of the organism's life time (requiring from minutes, to hours, to days to reach a new steady state) are termed acclimatory responses or acclimations. In the North American literature, the response is termed an acclimatization if it occurs naturally (where parameters other than the one of interest cannot be fully controlled). Only acute and acclimatory responses are possible within a given generation. However, all components of the cascade (from sensing and signal transduction to acclimatory response) can change through evolutionary time, a process defined in the literature as phylogenetic adaptation and illustrated in the lower panel (Hochachka and Somero, 1984). See text for further details. (B) The HVR shown for lowlanders and highlanders, indicating severe HVR blunting in the latter (data from Winslow and Monge, 1987).

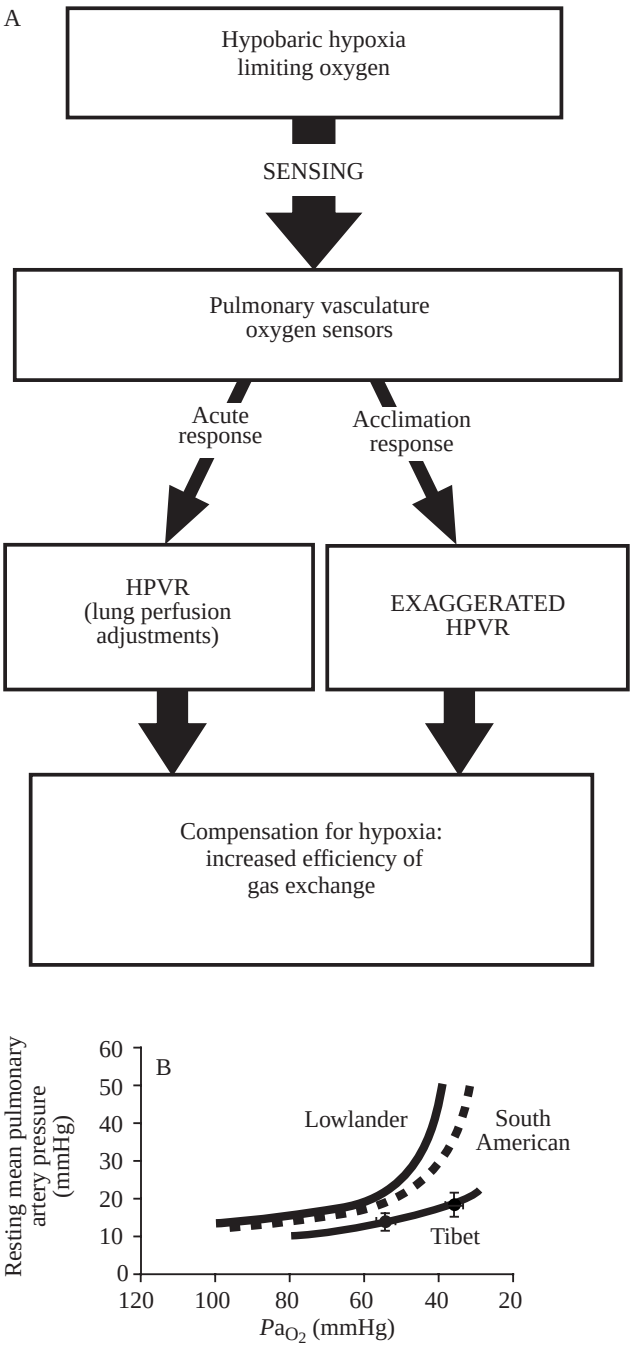
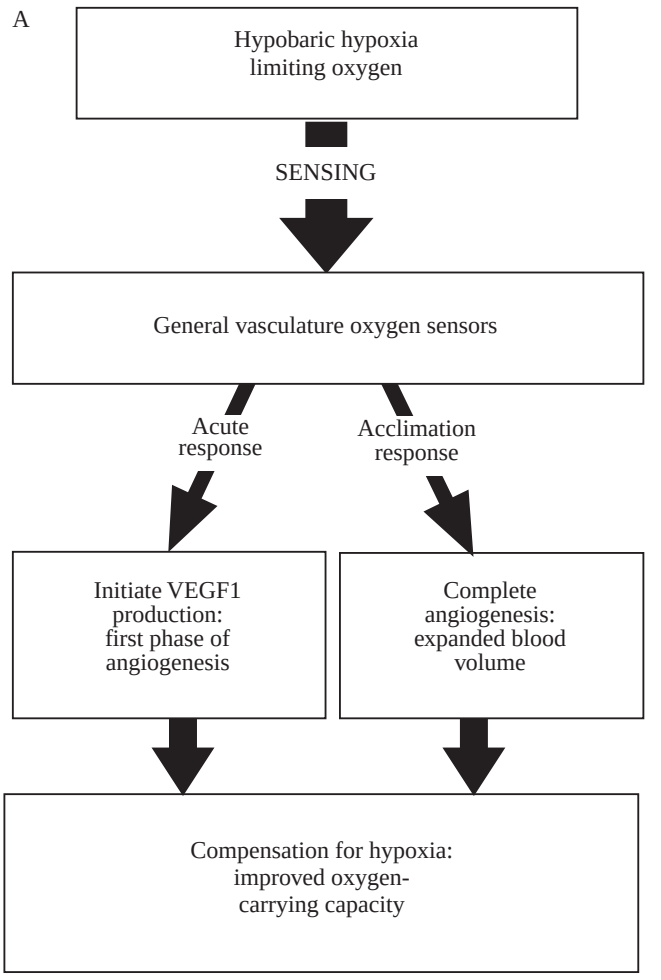


Fig. 2. (A) Diagrammatic summary of the formal relationships between time and the hypoxic pulmonary vasoconstrictor response (HPVR) to hypoxia. All components of the cascade (from sensing and signal transduction to acclimatory response) can change through evolutionary time, a process defined in the literature as phylogenetic adaptation and illustrated in (B). See text for further details. (B) The HPVR expressed as change in pulmonary artery pressure as a function of arterial oxygen tension (Pa_{O_2}) (data from Groves *et al.* 1993).



B

Angiogenesis

Altitude (m)	Total blood volume (ml kg^{-1})
0	85
3700	108
4500	110
4500 (CMS)	181

Fig. 3. (A) Diagrammatic summary of the formal relationships between time and hypoxia-exposure in the hypoxia-inducible factor 1 (HIF1)-mediated production of vascular endothelial factor 1 (VEGF1) and the initiation of angiogenesis. All components of the cascade (from sensing and signal transduction to acclimatory response) can change through evolutionary time; for example, the hypoxia-dependent increase in blood volume and red blood cell mass can be substantially greater in Quechuas than it is in Sherpas, in extreme cases leading to chronic mountain sickness (CMS or Monge's disease, more common in the former than in the latter). (B) Relationship between altitude and blood volume in Peruvian natives (data from Winslow and Monge, 1987).

hypertension (Heath and Williams, 1991), (iii) maintains angiogenesis (Heath and Williams, 1991; Harik *et al.* 1996), (iv) maintains erythropoiesis, further expanding the RBC mass (Winslow and Monge, 1987), and (v) allows metabolic reorganization, one expression of which is an increased carbohydrate preference during exercise (Brooks, 1998; Hochachka *et al.* 1996*b*). Typically, these acclimations take days to weeks to settle down at new steady states.

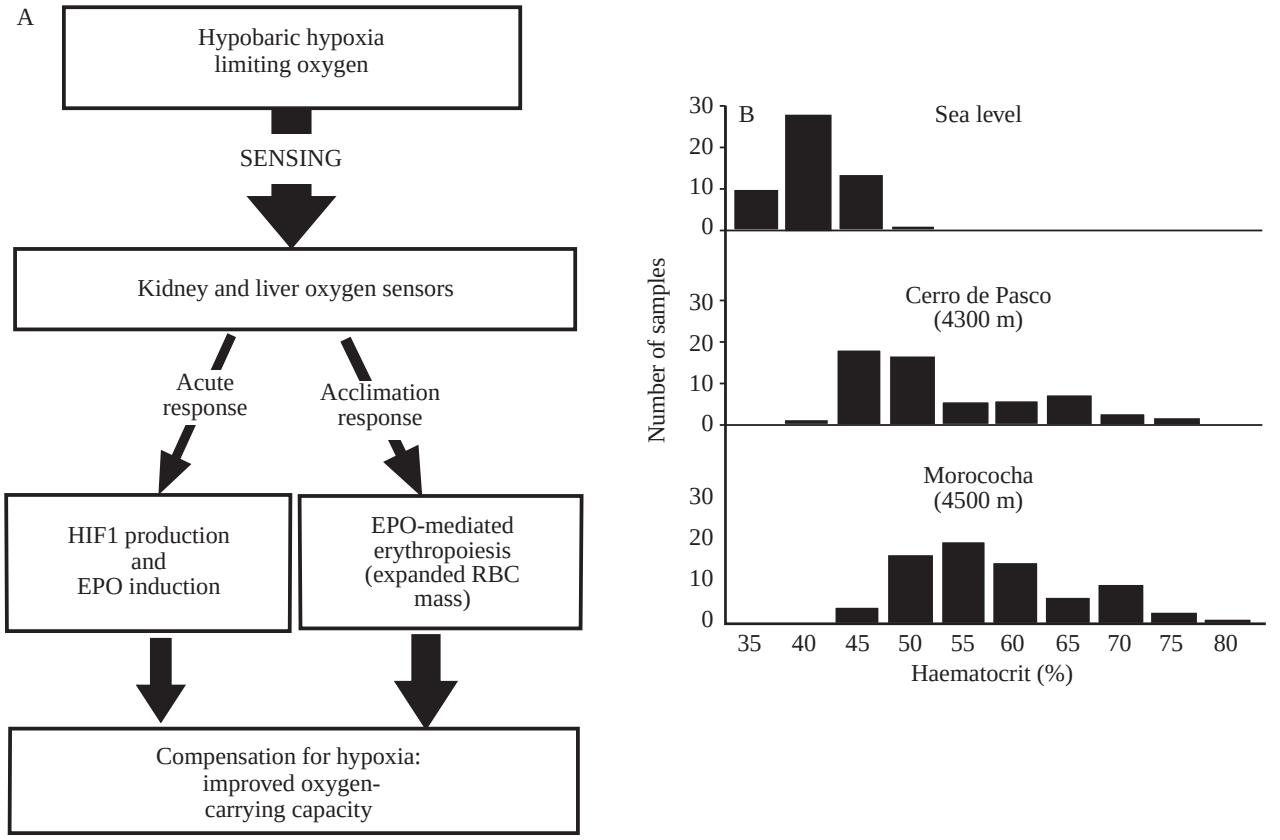


Fig. 4. (A) Diagrammatic summary of the formal relationships between time and hypoxia exposure in the hypoxia-inducible factor 1 (HIF1)-mediated production of erythropoietin (EPO) and the initiation of erythropoiesis. All components of the cascade (from sensing and signal transduction to acclimatory response) can change through evolutionary time. For example, the response is more robust in lowlanders and Quechuas than it is in Sherpas. See text for further details. (B) Representative data indicating the relationship between altitude and haematocrit (modified from Winslow and Monge, 1987). RBC, red blood cell.

In terms of compensating for the O_2 deficit of hypoxia, acclimations are better than acute adjustments. For example, after acclimation in lowlanders, $\dot{V}_{O_2max}$ is still affected by hypoxia, but to a lesser degree than previously. There is less deficit due to O_2 lack and less lactate accumulation (see West, 1986; Winslow and Monge, 1987; Heath and Williams, 1991). The attenuation of lactate accumulation despite maintained hypoxia has been perplexing to physiologists: because it was noted that the higher the altitude for acclimation, the lower the blood [lactate] during a given exercise protocol, the attenuation became known as the lactate paradox (Brooks *et al.* 1996; Hochachka *et al.* 1991). In the context of this analysis, the key insight is that essentially all acute hypoxia response systems in lowlanders can be further adjusted during acclimation (Brooks *et al.* 1996).

Acute and acclimation responses in indigenous highland lineages

To evaluate changes in these physiological traits through generational time, we compared the above acute and acclimatory patterns of lowlanders with those found in indigenous highlanders. These comparisons were guided by earlier studies of the diving response in pinnipeds, which identified two categories of (conservative *versus* adaptable) physiological characters utilized in orchestrating the evolution of this complex physiological system. Interestingly, current evidence indicates that ‘conservative’ and ‘adaptable’ physiological characters are also involved in human responses to hypoxia. Since we are assessing traits within a single species, conservative characters are dominant and are too numerous to outline in detail; three examples are haemoglobin (Hb) O_2-affinity and regulation (Winslow and Monge, 1987), muscle organization into different fibre types (Kayser *et al.* 1991; Rosser and Hochachka, 1994) and the brain’s almost exclusive preference for glucose as a fuel (Hochachka *et al.* 1995, 1996*c*). Such categories of physiological traits – in sum they make up most of our physiology – and the way they are used upon hypoxia-exposure appear common in humans no matter what the lineage or the O_2 content of the inspired air in the normal environment.

Despite the overwhelmingly conservative nature of human physiology, we also found evidence for numerous metabolic and physiological responses to hypobaric hypoxia that are similar in Quechuas and Sherpas. Such ‘adaptable’ characters seemingly occur at all levels of organization examined and

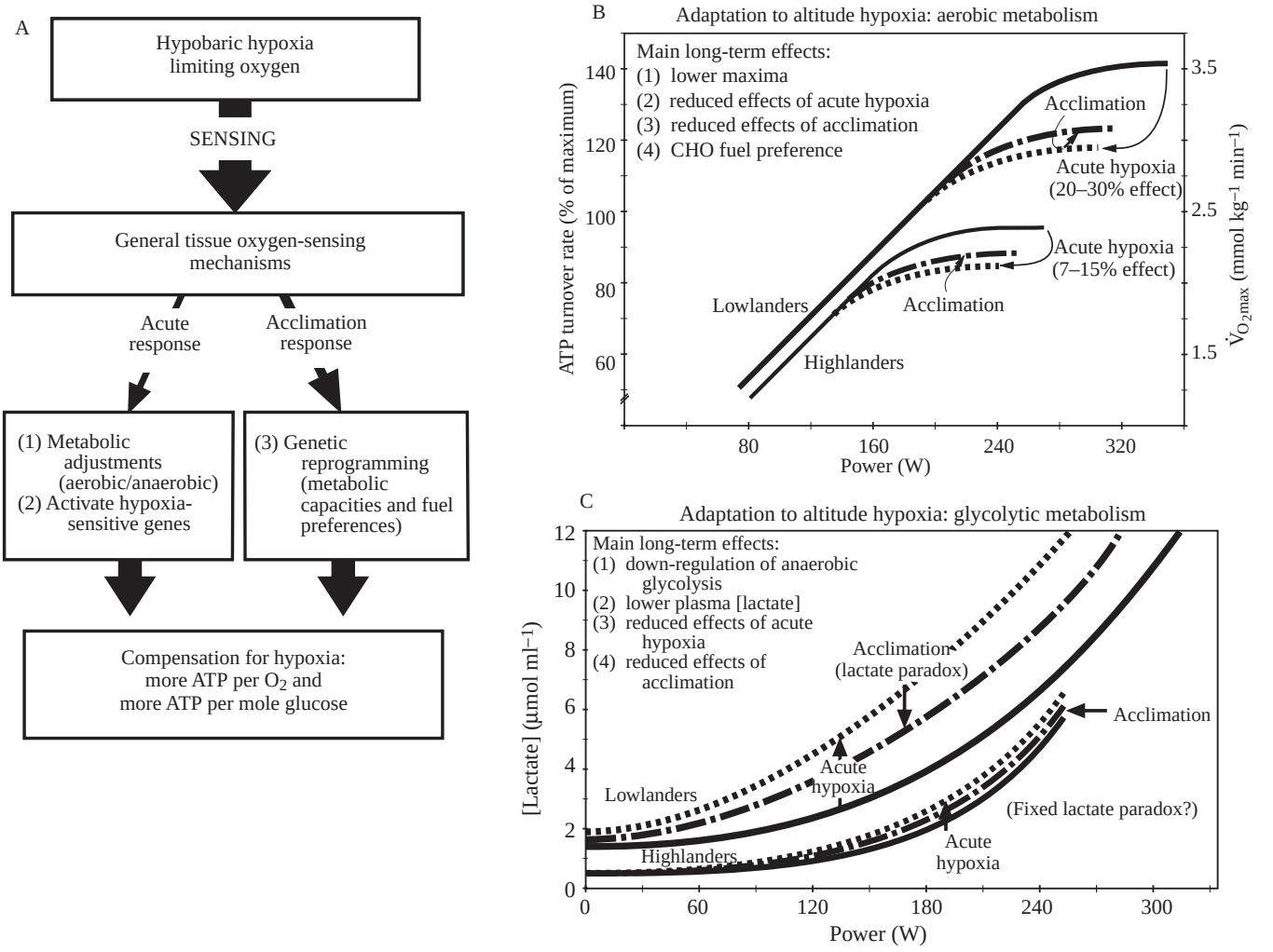


Fig. 5. (A) Diagrammatic summary of the formal relationships between time and hypoxia exposure in orchestrating exercise and metabolic responses to hypoxia. All components of the cascade (from sensing and signal transduction to acclimatory response) can change through evolutionary time; effects on aerobic and glycolytic contributions to whole-body exercise are illustrated in (B) and (C). (B) Effects of acute and acclimatory exposure to hypoxia on aerobic metabolism during exercise in two human lineages (lowlanders compared with Andean and Himalayan natives). Diagrammatic summary based on lowlander and Quechua data from Hochachka *et al.* (1991) and Matheson *et al.* (1991). The main long-term effects shown in the inset refer to metabolic responses in Quechuas. Adenosine triphosphate (ATP) turnover rates during exercise are standardized to Quechua data. (C) Effects of acute and acclimatory exposure to hypoxia on the plasma lactate response during exercise in two human lineages (lowlanders compared with Andean and Himalayan natives). Diagrammatic summary based on lowlander and Quechua data from Hochachka *et al.* (1991) and Matheson *et al.* (1991). The main long-term effects shown in the inset refer to metabolic responses in Quechuas. $\dot{V}_{O_2max}$, maximal rate of oxygen uptake.

can be summarized as adjustments in the above five loosely linked response systems which seem to form a key and common basis for the complex physiology of hypoxia-tolerance: (i) a blunted hypoxic ventilatory response mediated by the carotid body O_2 sensor, serving to counteract acid–base problems (Samaja *et al.* 1997) arising from hyperventilation (Fig. 1); (ii) a blunted hypoxic pulmonary vasoconstrictor response mediated by pulmonary vasculature O_2 sensor, serving to minimize risks of pulmonary hypertension (Fig. 2); (iii) up-regulated expression of VEGF1 (mediated by vascular O_2 sensors), angiogenesis and, hence, increased blood volume (Fig. 3), (iv) maintained EPO regulation of erythropoiesis (kidney O_2 sensors) and, hence, increased red blood cell mass and O_2-carrying capacity (Fig. 4), and (v) regulatory adjustments of metabolic pathways to alter fuel preferences, the ratio of aerobic/glycolytic metabolic pathways (Fig. 5) and, in striated muscle, to attenuate concentrations of enzymes involved in energy metabolism (for representative data, see Green, 1992; Hochachka, 1992; Hochachka *et al.* 1992; Kayser *et al.* 1991, 1994, 1996). These, in turn, set the stage for additional 'downstream' effects. For example, we find that, in Andean and Himalayan natives, maximum aerobic and anaerobic exercise capacities are down-regulated (Fig. 5). The acute effects of hypoxia (making up the energy deficit due to O_2 lack) expected from lowlanders are blunted (Brooks *et al.* 1996) and metabolic acclimation effects (Hochachka *et al.*

1991; Hochachka, 1996; Matheson *et al.* 1991) are also attenuated. The *in vivo* biochemical properties of skeletal muscles, in Quechuas formed predominantly of slow-twitch fibres (Rosser and Hochachka, 1994), are consistent with regulatory adjustments of glycolytic *versus* oxidative contributions to energy supply, thus improving the yield of ATP per mole of carbon fuel utilized (Hochachka, 1996). These fibre type distributions in indigenous highlanders are unchanged by acclimation (Kayser *et al.* 1996) and correlate with improved coupling between ATP demand and ATP supply pathways (lesser perturbation of phosphate metabolite pools during rest–exercise transitions (Allen *et al.* 1997; Hochachka and McClelland, 1997), lower levels of lactate accumulation (Hochachka *et al.* 1991) and improved endurance (Matheson *et al.* 1991). Indeed, the low level of lactate accumulation during exercise is one of the most characteristic metabolic features of indigenous highlanders (West, 1986; Hochachka, 1996). Kenyans native to medium-altitude environments, even if not as well studied (Saltin *et al.* 1995*a*,*b*), show similar, if higher-capacity, biochemical and physiological properties (adjustments at least in part based on a preponderance of slow-twitch fibres in skeletal muscles); this is not evident in Africans originating from lowland regions of West Africa, who show a much higher preponderance of fast-twitch fibres in their muscles (Ama *et al.* 1986). Heart adaptations also seem to rely upon stoichiometric efficiency adjustments (Hochachka *et al.* 1996*b*; Holden *et al.* 1995), improving the yield of ATP per mole of O_2 consumed (as in muscle) (Brooks, 1998; Brooks *et al.* 1991), by increased preference for carbohydrate as a

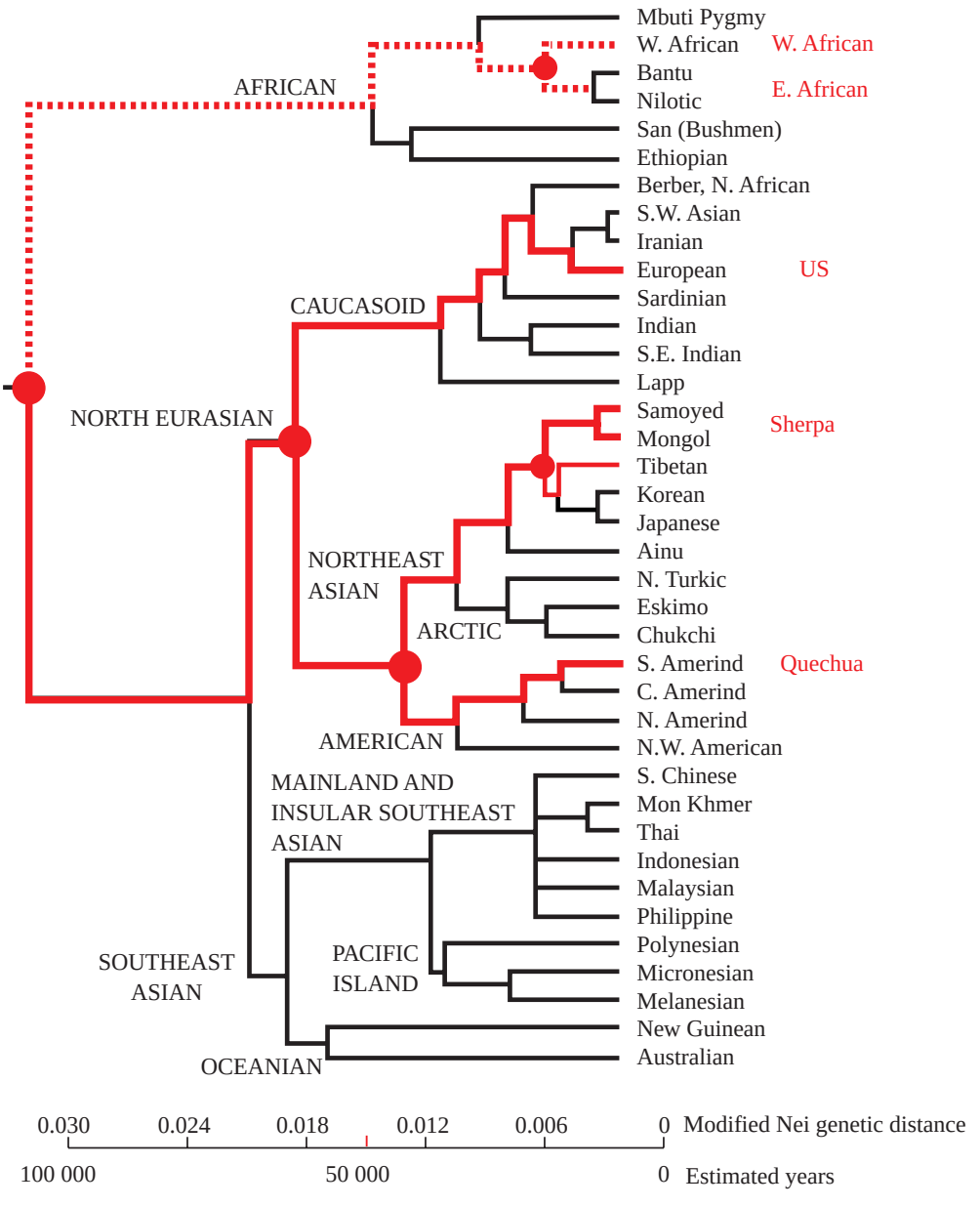


Fig. 6. An abbreviated phylogenetic tree of the human species as summarized by Cavalli-Sforza *et al.* (1994), with an estimated species age of 100 000 years included for temporal reference. Although our species age estimate is controversial, the actual value is not critical to the main argument presented. The four main groups for which detailed data are used for this analysis are shown on the right in red. The pathways tracing each of these lineages back in time are shown in red. Dashed lines are used for African lineages, for which fewer data are available. Filled circles identify nodes from which different lineages diverged: Sherpas *versus* Tibetans; Quechuas *versus* Sherpas; Caucasians *versus* Sherpas and Quechuas; West Africans *versus* East Africans; and African lineages *versus* all other lineages. Such phylogenetic analysis shows that the last time Caucasians shared common ancestors with Sherpas and Quechuas was over 50 000 years ago, approximately half the age of our species. Similarily, Sherpas and Tibetans last shared ancestors with Quechuas and Aymara some 30 000 years ago, approximately one-third of the age of our species. When east Africans are considered, common ancestry with Himalayan and Andean lineages goes back even deeper in phylogeny. Despite such distant divergences, all five high-altitude groups (Quechua, Aymara, Sherpa, Tibetan and Kenyan) show numerous similarities in physiological hypoxia defence mechanisms (see Fig. 7). See text for further details. Modified from Hochachka *et al.* (1997).

carbon and energy source. Together with increased blood volume and red blood cell mass (i.e. increased whole-body O_2-carrying capacity), these adaptations imply dampened heart work requirements at any given altitude for a similar submaximal level of whole-body exercise. Finally, a blunted catecholamine response to hypoxia in indigenous highlanders indicates a reduced hypoxic sensitivity of sympathadrenergic control (Antenzana *et al.* 1992, 1995; Mazzeo *et al.* 1991; Colice *et al.* 1993; Favier *et al.* 1996), below the normally expected desensitization upon exposure of human cells to hypoxia (Resink *et al.* 1996). Compared with acute or acclimatory adjustments, these longer-term (phylogenetic) adaptations appear to compensate pretty well for O_2 deficits caused by hypoxia, but this advantage appears to be gained at the cost of a notable attenuation of maximum aerobic and anaerobic metabolic capacities (Fig. 5). Thus, on balance, the picture emerging to this point is that of a high-altitude physiological phenotype based on numerous similar physiological traits (data based mainly on Sherpas and Quechuas).

Parenthetically, we might add that, while overall hypoxia responses appear to involve fine tuning of each of the above sensing and signal transduction pathway cascades, the hypoxia 'defence' adjustments of Andean and Himalayan natives are not always exactly the same. Of the above O_2-sensor-linked response systems, for example, the HVR is more robust in Tibetans than in Quechuas (Strohl and Beall, 1997) or Sherpas (Lahiri *et al.* 1969), while hypoxia-mediated increases in red blood cell mass (Hochachka *et al.* 1991, 1996*c*) in Andean natives are more robust than in Himalayans. Similarily, glucose metabolic rates are mildy down-regulated in the central nervous system (CNS) in Quechuas, hypometabolism apparently being used as a hypoxia defence strategy (Hochachka *et al.* 1995), but this trait is not expressed in Sherpas (Hochachka *et al.* 1996*c*). Given the length of time these lineages have been evolving separately (see below), such modest differences in a few physiological characters are not unexpected and do not alter our impression of a high-altitude physiological phenotype based on numerous similar traits in Quechuas and Sherpas.

Common phenotypes for hypoxia-tolerance and for endurance performance

An interesting possibility, that the adjusted hypoxia response systems (AHRSs) described above are loosely 'linked', is further supported by the fact that most of them are also found in humans adapted for endurance performance. This often includes a blunted HVR and HPVR, expanded blood volume, altered expression of metabolic enzymes and metabolite transporters, fuel preference adjustments, an enhanced ratio of aerobic/anaerobic contributions to exercise and, perhaps most notable of all, enhanced endurance (Brooks *et al.* 1996; Hochachka, 1994; Matheson *et al.* 1991; Saltin *et al.* 1995*a*,*b*). In endurance-trained athletes, who display much higher maximum aerobic capacities than do natives of high altitude, many of these series of traits appear as high-performance versions of those found in high-altitude natives, with up-regulation of muscle mitochondrial volume density (of O_2 flux capacities at the working tissues) being perhaps the only major modification to the physiological phenotype described above (for further literature in the exercise field, see Saltin *et al.* 1995*a*,*b*; for data on mitochondrial volume densities in highlanders compared with lowlanders, see Kayser *et al.* 1996). The comparisons shown in Fig. 5 of lowlanders and highlanders under normoxia are qualititatively good descriptions of the difference between individuals who are well-adapted for endurance *versus* those who are not. Low plasma lactate levels during exercise that elicits maximum aerobic metabolism is as characteristic of endurance performers as it is of highlanders (Brooks *et al.* 1996; Hochachka, 1994). Put another way, the biochemical and physiological organization of both indigenous highlanders and individuals adapted for endurance performance are similar to each other, but both differ strikingly from the homologous organization in 'burst performance' individuals (Brooks *et al.* 1996; Hochachka, 1994; Saltin *et al.* 1995*a*,*b*). Similar differences emerge when (either untrained or trained and elite) individuals from East Africa (medium-altitude origins; Saltin *et al.* 1995*a*,*b*) are compared with individuals of West African (lowland) origins, in whom fast-twitch fibres form a much larger percentage of skeletal muscle (Ama *et al.* 1986). In the latter, exercise-induced lactate concentrations can reach very high levels, and cardiovascular adjustments play as important a role in recovery from exercise as they do during exercise *per se* (Brooks *et al.* 1996).

Although genetic *versus* environmental contributions to these character traits are hard to quantify (most physiological studies are not properly designed to evaluate this issue), many workers assume that genetic factors account for approximately 50 % or more of the variance of these kinds of physiological systems (Ama *et al.* 1986; Fagard *et al.* 1991). What is more, the genetic contribution to any given trait, such as HVR, may vary in different lineages, being higher in Tibetans than in Andean natives, for example (Strohl and Beall, 1997; also compare the study of Tibetans by Kayser *et al.* 1996 with the study of Sherpas by Lahiri *et al.* 1969). It is axiomatic, of course, that natural selection can act only upon components that are under genetic influence.

The phylogenetic connection

If the AHRS constitutes the primary 'solution' of our species to 'problems/requirements' of hypobaric hypoxia and/or endurance performance, the question arises of whether the same 'solution' has arisen more than once in our species history – this would be good evidence for evolutionary adaptation. Assessing such evidence requires insight into the evolutionary pathways of our species. Accordingly, we set up a simplified 'phylogenetic tree' for the human species (Fig. 6) from an extensive summary of human genetics and evolution

by Cavalli-Sforza *et al.* (1994). As emphasized elsewhere (Hochachka *et al.* 1997), key environmental influences on the root of this sort of phylogeny, on the origins of our species, go back a long way. Over a time span of approximately 3 million years, from 4 to 1 million years ago, several different australopithecines thrived along the East African Rift Valley system under challenging environmental conditions (Bishop, 1978; Hamilton, 1982; Jones, 1995; Maglio and Cooke, 1978). A topographical profile along the equator from the west (Atlantic) to the east coast approaches 2000 m crossing the central Rift Valley regions (Vrba, 1994), an altitude easily high enough – and possibly ideal from the athletic training point of view (Levine and Stray-Gunderson, 1997) – for physiological response and adaptation (Winslow and Monge, 1987). Recent geological data suggest that the fastest uplifting of this Rift Valley system occurred during the last 2 million years (Bishop, 1978) and led to diversification of local climates (colder, drier, higher) and of primate/hominid lineages (Maglio and Cooke, 1978). Even in the Hadar Region, which actually belongs to the lower part of the Rift Valley system, australopithecines lived for at least 1.5 million years, from 4 million to 2.5 million years, at a moderate altitude of approximately 1000 m (Jones, 1995). Additionally, at least nine important glaciations during the last 0.7 million years are believed to have influenced the Rift Valley region (Coppens *et al.* 1976); these cold oscillations were apparently as pronounced between 2 million years and 0.7 million years ago as subsequently (Hamilton, 1982). Finally, seasonal variations and food resource patchiness during the last several million years in the Rift Valley region are consistent with increasing endurance performance requirements for food foraging; extant hunter-gatherers routinely forage over ranges of 20–50 km per day (Schrenk, 1977; Vrba, 1994). Thus, it is tempting to characterize early phases of hominid evolution in the East African Rift as occurring under conditions of mild altitude-hypoxia aggravated by drier and colder climates. These conditions prevailed for the ancestors of our species, they prevailed at the origins of our species and indeed they prevail in East Africa today. Could these conditions have influenced the evolution of human physiology and led to the appearance of the hypoxia-tolerance/endurance performance phenotype in the first place?

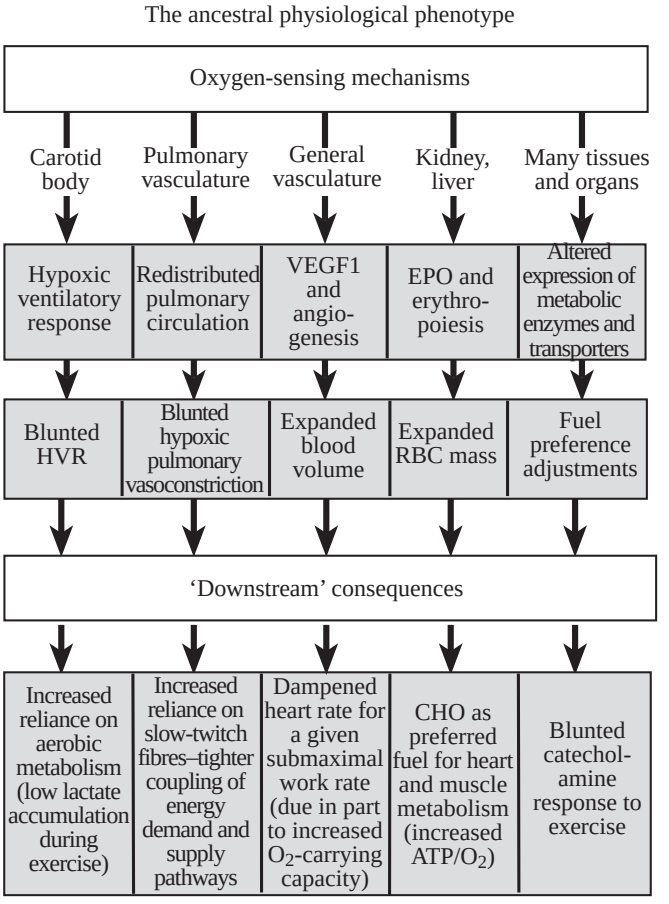


Fig. 7. A diagrammatic summary of adjusted hypoxia response systems (the AHRS) proposed as the ancestral physiological phenotype and as a phylogenetic adaptation to hypobaric hypoxia. The summary is based largely upon studies of Quechuas and Sherpas. Essentially all of the characteristics summarized here are also expressed in individuals well-adapted for endurance performance. In the latter, the main modification involves an up-regulation of mitochondrial volume densities at the working tissues (altered expression of mitochondrial metabolic enzymes and metabolite transporters), which is why this is referred to as a 'high-capacity' version of the lower-capacity high-altitude phenotype. See text for further details. Modified from Hochachka *et al.* (1997). HVR, hypoxic ventilatory response; EPO, erthropoietin; RBC, red blood cell; VEGF1, vascular endothelial factor 1; CHO, carbohydrate.

The main groups whose physiological responses to hypobaric hypoxia to date have been extensively studied are (i) lowland Caucasians and Asians, (ii) Sherpas and Tibetans of the Himalayan plateau, and (iii) Quechuas and Aymara of the Andean range (Winslow and Monge, 1987; Moore *et al.* 1992; Hochachka, 1996). A few new studies of west Africans contrasted with east Africans indigenous to medium altitudes are also now available (Saltin *et al.* 1995*a*,*b*). If we assume that our species age is approximately 100 000 years old (this is controversial, but if our species is even older, the arguments below will be even stronger), then a close examination of Fig. 6 is instructive. First, it suggests that the last time Caucasians, Sherpas and Quechuas shared common ancestors was impressively long ago: approximately half the age of our species. Second, the last time the Himalayan highlanders (Sherpas and Tibetans) and the Andean highlanders (Quechuas and Aymaras) shared common ancestors was some 30 000 years ago – a period equivalent to approximately one-third of the history of our species. Third, divergence times between these groups and East Africans from medium-altitude environments are even greater. Despite the distant divergences of the latter three – the Andean, the Himalayan and the East African – lineages, many of their metabolic and physiological responses to hypobaric hypoxia are similar. Fourth, in numerous other lineages (including intermediate branches in the phylogenetic tree shown in Fig. 6), the AHRS features are known not to be as dominant as in Quechuas and Sherpas,

where AHRS expression is pretty well the norm. These provocative phylogenetic data are consistent with two possible interpretations.

Ancestral phenotype hypotheses

(i) One plausible possibility is that, with only modest differences, the same metabolic and physiological 'solution' arose independently by positive natural selection in the two high-altitude (Quechua and Sherpa) lineages for which we have the most data and possibly in a third east African lineage for which the data are not as extensive. If so, these comparisons would satisfy at least one of the criteria of evolutionary biology and would strongly support the conclusion that the suite of physiological characters described above are defence adaptations against hypobaric hypoxia and arose by positive selection. Whereas this was our thinking initially, the 'low-capacity *versus* high-capacity phenotype' observations noted above are not easily incorporated into this hypothesis.

(ii) A second hypothesis is that this suite of physiological and metabolic traits, the AHRS, while arising as described above by positive natural selection, represents the 'ancestral' condition (Fig. 7), which would be consistent with the evidence suggesting that the origin of our species occurred under conditions that were getting colder, drier and higher. According to this model, over some 5000 or more generations of our species history, this condition was 'retained' in a down-regulated low-capacity form in high-altitude groups (Sherpas, Tibetans, Quechuas, Aymaras) and was 'retained' in an up-regulated high-capacity form (probably in many) groups selected for endurance performance (including Kenyan highlanders, who continue to thrive on the same plateau that served as the colder, drier and higher birthplace of our species). In high-altitude populations, the ancestral physiological condition was fine-tuned: for example, muscles with down-regulated mitochondrial volume densities (Kayser *et al.* 1996) for 'life in the slow lane' (low maximum aerobic metabolic capacities) under hypobaric hypoxia. In groups selected for endurance performance, the ancestral physiological condition in relative terms involved high-capacity energy supply pathways being fine-tuned for the high-capacity energy demand of sustained physical activity. In situations such as the moderate hypobaric hypoxia of East Africa, selection pressures for both hypoxia-tolerance and endurance performance may well have been applied simultaneously (for a recent detailed analysis of the interaction between endurance performance and hypobaric hypoxia, see Levine and Stray-Gunderson, 1997). In any event, the second hypothesis predicts that the ancestral organization of our physiology (Fig. 7) was inherently very dependent upon efficient physiological O_2 delivery systems and upon 'aerobic' metabolic pathways and fibre types, with relatively minor development of, or reliance on, anaerobic metabolic systems to sustain short, intense bursts of whole-body exercise.

If this analysis is correct, then (in terms of our original framework for evaluating the evolution of complex physiological systems) it appears that much is determined by so-called initial or ancestral conditions. Much of the evolution of physiological systems apparently involves balancing selection (pruning out genotypes in which the ancestral 'models' are altered). Only a part of the evolution of our physiology seems to be the result of positive selection for new functional capacities and fundamentally new physiological characters – the AHRS described above (Fig. 7). This amplifies our understanding of this physiological phenotype for, as biologists have long realized, our discipline generates two kinds of explanations. At one level, we discover how things work; we discover mechanisms. At another level, we discover where these mechanisms came from; we discover their origins and their history. Neither kind of explanation is complete by itself; each needs the other.

That is why elsewhere (C. P. Mangum and P. W. Hochachka, in preparation) we have argued that a blending of evolutionary and mechanistic physiology is our preferred goal for the future of our discipline.

This work was supported by the NSERC (Canada).

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