BIOCHEMISTRY OF ACUTE AND CHRONIC HYPOXIA

EVOLUTION OF HYPOXIA TOLERANCE: DIVING PINNIPED MODEL AND HUMAN HYPOBARIC HYPOXIA MODEL

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RESUMEN: Evolución de la Tolerancia a la Hipoxia: el Modelo de Pinnipedo Buceador y el Modelo Humano de Hipoxia Hipobárica

Para los fisiólogos, el término "adaptación" usualmente se refiere a cualquier rasgo considerado ventajoso; los biólogos evolutivos restringen el término para los rasgos que se originan y se mantienen por selección. Según su definición, muchos rasgos fisiológicos pueden meramente reflejar herencia transmitida por generaciones. Al considerar la evolución de la tolerancia a la disponibilidad reducida de oxigeno, hemos estudiado los pinnípedos, en los que hay dos grupos dominantes, phocids y otariids que varian en sus capacidades de buceo, y generaciones humanas expuestas por varios tiempos generacionales a hipoxia hipobárica. Los principios básicos de la evolución de los sistemas fisiológicos complejos emergieron primero del análisis de la respuesta de buceo. Luego analizamos las respuestas del ser humano a la hipoxia hipobárica en tres grupos: nativos de nivel del mar, nativos Andinos (Quechuas) y nativos de los Himalayas (Sherpas). Como en el ejemplo de los pinnípedos, encontramos caracteres fisiológicos 'conservadores' y 'adaptables' implicados en las respuestas humanas a la hipoxia. Los caracteres 'conservadores'son claramente dominantes y son muy numerosos para delinearlos en detalle; tres ejemplos son la afinidad de la hemoglobina, la organización muscular en diferentes tipos de fibras, y la preferencia casi exclusiva que tiene el cerebro por la glucosa como un combustible. Es muy notable que también encontramos evidencia de caracteres 'adaptables' a todos los niveles de organización examinados. Al nivel corporal total en Quechuas y Sherpas, encontramos (i)que las máximas capacidades de ejercicio aeróbicas y anaeróbicas tenían "desensibilización", (ii) que el efecto agudo de la hipoxia (compensador del déficit de energia debido a la carencia de oxigeno, i.e. el efecto Pasteur) esperado de los nativos de nivel del mar estaba atenuado, y (iii) que los efectos de la aclimatación estaban también atenuados. La conducta bioquímica de los músculos esqueléticos fue congruente con un menor uso de la glicólisis anaeróbica como fuente de energia, resultando así en un un mejor rendimiento de ATP por mol de carbono utilizado. Las adaptaciones del corazón también parecieron depender de ajustes de eficiencia estoiquiométrica, mejorando el rendimiento de ATP por mol de oxigeno consumido (usando de preferencia la glucosa en lugar de los ácidos grasos). La mayoría de las adaptaciones bioquímicas y fisiológicas que notamos (ya sea como respuestas agudas o como respuestas de aclimatación) fueron similares en Sherpas y Quechuas. Estos dos grupos no han compartido un ancestro común por más o menos 1/3 de la historia de nuestra especie, de manera que asumimos tentativamente que sus rasgos fisiológicos similares se originaron independientemente como adaptaciones de defensa a la hipoxia en dos tiempos y lugares diferentes de nuestra historia. Al igual que en la evolución de las delicadas capacidades para el manejo del oxigeno cada vez más escaso en los animales buceadores, la evolución de la tolerancia humana a la hipoxia puede ser descrita en términos de cómo dos categorias de caracteres fisiológicos (conservadores vs adaptables) son ensamblados en diferentes linajes humanos y cómo cambia el ensamblaje a través de generaciones. Evidencias más recientes que indican que nuestra especie ha evolucionado bajo condiciones 'más frias', 'más secas' y 'de más altitud', sugieren que estas adaptaciones pueden representar la condición fisiológica 'ancestral' para los humanos.

Palabras claves: Hipoxia, Hipobaria, Fisiología evolutiva, Fisiología del buceo, Mamíferos marinos, Adaptación a la altura

RÉSUMÉ: Evolution de la tolérance à l'hypoxie : le modèle du pinnipède plongeur et le modèle humain d'hypoxie hypobare.

Pour les physiologistes, le terme "adaptation" se réfère généralement à n'importe quel caractère considéré avantageux. Les biologistes évolutifs restreignent le terme aux caractères qui apparaissent et subsistent par sélection. Selon leur définition, de nombreux caractères physiologiques peuvent être le simple reflet de l'héritage transmis à travers les générations. Considérant l'évolution de la tolérance à une disponibilité réduite en oxygène, nous avons étudié les pinnipèdes dont les deux groupes dominants, les phocides et les otarides, présentent des capacités variables de plongée, et les lignées humaines exposées à l'hypoxie hypobare pendant des périodes générationnelles variables. Les principes de base de l'évolution des systèmes physiologiques complexes ont surgi d'abord de l'analyse de la réponse de plongée. Nous avons analysé ensuite les réponses de trois groupes humains à l'hypoxie hypobare : natifs du niveau de la mer, natifs des Andes (Quechuas) et natifs des montagnes de l'Himalaya (Sherpas). Comme chez les pinnipèdes, nous rencontrons des caractères physiologiques "conservateurs" et "adaptables" intervenant dans les réponses de l'être humain à l'hypoxie. Les caractères "conservateurs" dominent nettement et sont trop nombreux pour que l'on puisse les définir de façon détaillée; trois exemples en sont l'affinité de l'hémoglobine avec l'oxygène, l'organisation musculaire dans différents types de fibres et la préférence quasi exclusive du cerveau pour le glucose comme combustible. De même, la présence de caractères "adaptables" à tous les niveaux

d'organisation examinés est tout à fait remarquable. Au niveau corporel total nous avons trouvé chez les Quechuas et les Sherpas, (1) que les capacités maximales d'exercice aérobique et anaérobique étaient "down-regulated"; (2) que l'effet aigu de l'hypoxie (compensant le déficit d'énergie dû au manque d'oxygène, p. ex. l'effet Pasteur) auquel on pouvait s'attendre chez les natifs du niveau de la mer était atténué; (3) que les effets de l'acclimatation étaient également atténués. Le comportement biochimique des muscles squelettiques était congruente à la moindre utilisation de la glycolyse anaérobique comme source d'énergie, dont le résultat était un meilleur rendement de l'ATP par mole de charbon utilisé. Les adaptations du coeur paraissaient dépendre également d'ajustements de l'efficience stoechiométrique, améliorant le rendement de l'ATP par mole d'oxygène consommé (en utilisant le glucose de préférence aux acides gras). La majorité des adaptations biochimiques et physiologiques observées (que ce soit comme réponses aiguës ou réponses d'acclimatation) ont été les mêmes chez les Sherpas et les Quechuas. Ces deux groupes n'ayant pas partagé d'ancêtre commun pendant environ un tiers de l'histoire de notre espèce, nous présumons que leurs caractères physiologiques similaires sont apparus de façon indépendante, comme des adaptations de défense face à l'hypoxie, à des époques et dans des lieux différents. De même que dans l'évolution des très fines capacités d'utilisation de l'oxygène s'affaiblissant de plus en plus chez les animaux plongeurs, l'évolution de la tolérance humaine à l'hypoxie peut être décrite de la façon suivante : comment deux catégories de caractères physiologiques (conservateurs vs adaptables) sont assemblés en différentes lignées humaines et comment l'assemblage change à travers les générations. Les preuves les plus récentes indiquant que notre espèce a évolué dans des conditions "de froid plus intense", "de plus grande sécheresse" ou "d'altitude plus élevée", suggèrent que ces adaptations peuvent représenter la condition physiologique "ancestrale" pour l'être humain.

Mots-clés : Hypoxie, Hypobarie, Physiologie évolutive, Physiologie de plongée, Mammifères marins, Adaptation à l'altitude.

SUMMARY: To physiologists, the term 'adaptation' usually refers to any trait which is considered advantageous; evolutionary biologists restrict the definition 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 studied the pinnipeds where the two dominant groups, phocids and otariids, varying in diving capacities, and human lineages exposed for varying generational time periods to hypobaric hypoxia. Basic principles of evolution of complex physiological systems first emerged from 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 hemoglobin oxygen affinities, muscle organization into different fiber 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 anaerobic glycolytic contributions to energy supply, thus improved yield of ATP per mole of carbon fuel utilized. Heart adaptations also seemed to rely upon stoichiometric effficiency 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 acclimation responses) were similar in Sherpas and Quechuas, These two lineages have not shared a common ancestor for about 1/3 of our species history, so we tentatively assume that their similar physiological traits arose independently as hypoxia defense adaptations in two different times and places in our history. As in the evolution of exquisitve capacities for management of oxygen down to vanishing low levels in diving animals, the evolution of human hypoxia tolerance can be described in terms of how two (consesative vs 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, Hypobaria, Evolutionary physiology, Diving physiology, Marine mammals, Altitude adaptation

INTRODUCTION

High altitude physiologists commonly assume that the functional responses to hypobaric hypoxia in humans represent hypoxia defense 'adaptations'. To the field of physiology an 'adaptation' - or an 'adaptive' trait - is rather loosely defined as any character whose structure or function improves chances of survival. While admitting that many such traits so identifed by physiology are 'true' adaptations, evolutionary biologists are somewhat more demanding in their criteria. By their definition, a trait can correctly be termed adaptive (i) if it arises by natural selection or (ii) if it is maintained by natural selection - or (iii) if both conditions are realized. By these criteria, many so-called physiological adaptations of humans might simply be ancestral or plesiomorphic traits, inherited and passed on in phylogeny. Since the precise combinations of such active and relatively passive processes may vary, the evolution of complex physiological systems might proceed along complex unexpected trajectories, rather than being directionally selection-driven down simple linear phylogenetic pathways. Hence, human hypoxia defense adaptations can be properly evaluated only in the context of their phylogeny. In considering the evolution of hypobaric hypoxia defense adaptations in humans what seemed to be required was a framework - or rules - by which complex physiological systems evolve. Our first insight into such a framwork arose from studies of the evolution of the diving response in marine mammals, so this is where we shall start.

The Diving Response in Marine Mammals

Although biologists have been intrigued by diving mammals and birds for well over a century, the physiological and metabolic mechanisms now known to permit an air breathing animal to operate successfully deep into the water column were first exposed in the 1930s and 1940s through the pioneering work of Scholander, Irving, and their colleagues (Scholander, 1940; 1963). The basis of their work provided the fundamental foundations of diving physiology, which are now known to include three key physiological 'reflexes': (i) apnea, (ii) bradycardia, and (iii) vasoconstriction and thus hypoperfusion of most peripheral tissues. Scholander referred to these physiological reflexes in combination as the 'diving response', and, in simulated diving under controlled laboratory conditions, he imagined the marine mammal reducing itself to a 'heart, lung, brain machine'. The metabolic representation of this response included the gradual development of oxygen limiting conditions in hypoperfused (ischemic) tissues, with attendant accumulation of end products of anaerobic metabolism (especially lactate and H^+ ions).

Scholander and many students following in his path observed that the key features of the diving response were evident in many different kinds of animals. Diving bradycardia was often used as a kind of index or indicator of the diving response and it was so seemingly universal among the vertebrates that Scholander (1963) referred to it as the 'master switch of life'. In his day, this 'master switch', or the diving response, was viewed as an obvious 'physiological adaptation' to diving, even if there was little indication as to how the response evolved through any particular lineage. At this time, little attention was paid to the criteria of evolutionary biology: that to be defined as adaptive a character either had to have arisen by natural selection or to be maintained by selective forces.

The advent of modern field study technologies, especially of microprocessor-assisted monitoring of aquatic animals while diving voluntarily in their natural environment (Guppy *et al.* 1986; Hill *et al.* 1987), has confirmed over the last two decades the validity and plasticity of the overall 'diving response' first elucidated in the 1930s and 1940s and has extended the list of key components. For the large seals (the champion divers of the marine mammal world, capable of diving for up to 2 hours at a time to depths of up to 1.5 km!), the major functional characteristics for such sensational diving capabilities include:

(1) apnea, with exhalation upon initiation of diving (for minimizing buoyancy and other pressure-related problems)

(2) bradycardia (in 1: 1 proportion with changes in cardiac output),

(3) peripheral vasoconstriction and hypoperfusion (in order to conserve oxygen for the central nervous system (CNS) and heart),

(4) hypometabolism of (vasoconstricted) ischemic tissues (also in order to conserve oxygen and plasma borne fuels for the CNS and heart).

(5) an enhanced oxygen carrying capacity (enlarged blood volume, expanded red blood cell mass within the blood volume - i.e. higher hematocrit (Hct), higher hemoglobin concentration ([Hb]) in red blood cells, and possibly higher myoglobin concentration ([Mb]) in muscles and heart), and

(6) an enlarged spleen (for regulating the Hct so that a very high 96 of RBCs need not be circulated under all physiological conditions). Additionally

(7) it should be noted that, for really outstanding diving, all of the above characteristics (i) are incorporated with a large body weight (in order to maximize the amount of oxygen that can be carried while minimizing mass-specific energy demands during diving by allometric effects), and (ii) are coupled with slow swimming speed while at sea (to minimize the cost of locomotion while maximizing submergence. hence foraging,. time).

The evidence for these overall patterns arises from studies of several phocid species (for example, see Kooyman et al. 1980; Kooyman, 1985; Guppy et al. 1986; Qvist et al. 1986; Castellini et al. 1992; Hindell et al. 1992; Thompson and Fedak, 1992; Reed et al. 1994; Hochachka et al. 1995; Hurford et al. 1995; Guyton et aL 1995; Butler et al. 1995).

The seals or phocids are one major branch of the pinnipedia; the other major branch, the otariids (sea lions and fur seals) are not as capable divers. When examined closely, however, essentially all of the above traits are also observable in otariids - but not all as amply expressed (see Hochachka and Mottishaw, 1996). Are all these traits 'adaptations' as commonly assumed by physiologists in this area?

Tracing the Evolution of Diving Capacity

To answer this question, what is required is a more

quantitative comparison of diving strategies within the phocids and otariids. When we tried to do this, we encountered two unexpected 'problems'. The first was that numerous physiological characteristics of diving animals - *instead of systematically varying with diving capacities* - were similar in all diving species for which we could find data. For example, values of maximum diving bradycardia (with concurrent peripheral vasoconstrictions) show no consistent phylogenetic patterns or relationship with diving duration. Since even some humans can turn down their heart to below 6 beats per min (Arnold, 1985), it perhaps should not be surprising that most divers can depress heart rate to a few beats per min (the 'floor board' for this function?). This could mean that heart rate is too crude a measure of circulatory control during diving and recovery (and its uniform control is consistent with the basic reflex being nearly universally present in some form in all vertebrates). Or, it could mean that heart rate control is 'conservative' or 'constrained' in evolution due to roles in so many different biological settings that any adaptational changes for diving are too modest to detect with the crude physiological criteria thus far utilized.

Interestingly, a similar situation seems to hold for another physiological character diving hypometabolism which we initially expected to vary with dive time. In earlier studies, we (Guppy et al. 1986; Hochachka and Guppy, 1987; Hochachka and Foreman; 1993) and others (Le Boeuf et al. 1989, 1992; Costa, 1991, 1993; Hindell et al. 1992) explicitly or implicitly assumed that the impressive diving performance of large seals depended in large part on an 'energy conserving' physiology and diving strategy. Central to this was some concept of diving hypometabolism. Subsequent research has uncovered two potential underlying mechanisms: (i) One hypothesis is that hypoperfusion (vasoconstriction) of nonworking peripheral muscles and other tissues is the proximate cause of hypometabolism, with reduction in tissue metabolic rate being a direct function of the reduction in oxygen delivery, a relationship also observed in terrestrial mammals (Hochachka, 1992; Guyton et al. 1995; Hochachka *et al.* 1995a). (ii) An alternate postulate is that regional hypothermia contributes to low metabolic rates, with metabolic suppression being a function of tissue cooling (Hill *et al.* 1987; Andrews *et al.* 1994). While these two mechanisms are not mutually exclusive, it was at first thought that the physiological characteristic of hypometabolism would be largely restricted to the large seals, or at least to phocids. However, recent careful experimental studies with sea lions (animals trained to remain submerged and relatively inactive for defined time periods) indicate that the metabolic rate declines as a direct function of diving duration; the metabolic rate for seven minute diving periods (water temperature at about 15°C) falls to about 50% of resting metabolic rate (RMR). Since the times involved are so short, it is unlikely that regional hypothermia plays a significant role in this metabolic suppression (Hurley, 1996). We interpret this to mean that activation of the diving response automatically leads to hypoperfusion of some tissues/organs and subsequently to diving hypometabolism. On its own, then, this physiological character, like bradycardia, would appear to be general among pinnipeds and thus could not be expected to vary (and indeed did not vary) in any systematic way with diving capacity.

The second unexpected 'problem' we encountered was purely practical. Ideally, for tracing the evolution of the diving response in these lineages, one would like to be able to compare all of the above metabolic and physiological characters in numerous phocid and otariid species. However, in reality, detailed information on complex characters such as tissue specific regional hypoperfusion is available for only a few species, so for multiple species comparisons (between phocids and phocids vs otariids), our analysis had to be restricted to only a few data sets: (i) body weight, (ii) spleen weight, and (iii) whole body hemoglobin (defined as the content of Hb in the entire blood volume of the organism).

In terms of diving capacity, the data for phocids were particularly clear. Thus, body weight influences the total onboard oxygen supplies as well as mass-specific energy demands; thus it would be expected - and was found - to vary with diving capacity. The spleen acts as a SCUBA tank (oxygenated red blood cell storage) (Ovist et al. 1986; Hurford et al. 1995). The spleen is controlled by a catecholamine-based regulatory circuitry which also controls several other metabolic and physiological functions during diving-recovery cycles (Hurford et al. 1995; Hochachka et al. 1995a; Lacombe and Jones, 1991). We anticipated and found that spleen weight also varies with diving abilities. Finally, whole body hemoglobin is a direct measure of oxygen carrying capacity; since maximum diving duration is presumably set by some complex balance between oxygen availability and oxygen demand, this too was expected and was found to respond to selection based on diving behaviour (see Hochachka and Mottishaw, 1996, for further discussion of these data).

Diving and Phylogeny

Taken together, the characters we analyzed reflect most of the known components of the diving response and they clearly fell into two kinds of categories - conservative vs adaptable. Included in the former are a number of diving 'characters' showing little variation in phocids and otariids, such as diving apnea, bradycardia, and regulated redistribution of cardiac output. The universality of such diving response traits, the fact that they can be elicited in terrestrial mammals including man (Arnold, 1985), suggests the possibility that their occurrence in diving animals is less 'an adaptation' for diving than it is a plesiomorphic or ancestral trait that simply preadapted air breathing vertebrates for dealing with a variety of stressful situations, including diving.

In contrast, the physiological characters which do vary, not only differ qualitatively between the pinniped lineages in the expected direction, but even more quantitatively correlate with dive time in phocids. Although our analyses do not expose causes (they expose correlations), these traits are the probable 'adaptations' accounting for the differences in diving capabilities observed in pinnipeds. Our analysis thus is consistent with the hypothesis that increased expressions of any of at least three factors - (i) body weight, (ii) spleen weight (independent of body weight) and (iii) whole body Hb (also independent of body weight) - are adaptations for extending diving duration in Phocids.

Interestingly, none of the above diving traits correlated as well with diving capacity in the sea lions and fur seals. While the apparent lack of significant correlations within otariids may be a simple artifact of the available data, three other possibilities are (i) that we did not have enough data for otariid species to reach the statistical power required, (as is probably the case in body weight vs. dive time), (ii) that variation in otariid maximum diving duration is not large enough for our relatively insensitive diving response characters to decipher any adaptive trends, (otariids are more closely related than phocids and may be less variable as a consequence), or (iii) that the evolution of the otariids has been 'driven' by factors other than requirements for long duration diving (such as reproductive requirements (Costa, 1991, 1993)).

Emerging Principles of Evolution of Physiological Systems

From the quantitative analysis of the variability of the diving response in pinnipeds (Hochachka and Mottishaw, 1997; Mottishaw, 1997; Mottishaw and Hochachka, 1997) three principles of evolution of the diving response emerged which may be generally applicable to the evolution of complex physiological systems.

1. A number of physiological/biochemical characters considered necessary in diving animals are conserved in all pinnipeds; these traits, which are necessarily similar in phocids and otariids, include diving apnea, bradycardia, tissue hypoperfusion, and hypometabolism of hypoperfused tissues. At this stage in our understanding of diving physiology and biochemistry, we are unable to detect any correlation between these characters and diving capacity.

2. A number of physiological/biochemical characters are more malleable and are clearly correlated with long duration diving and prolonged foraging at sea. These characters are more lineage specific, and, for the phocids include body weight, spleen weight, and whole body oxygen carrying capacity. Within the phocids, the larger these are, the greater the diving capacity (defined as diving duration). Since the relationships between diving capacity and spleen weight or between diving capacity and whole body oxygen carrying capacities are evident even when corrected for body weight, it is reasonable to suggest that the two traits - large spleens and large whole body oxygen carrying capacities extend diving duration. That is, in contrast to conserved traits such as bradycardia, these characters (and presumably other similar ones, such as tissue specific metabolic organization (Hochachka and Foreman, 1993)) have evolved to enable prolonged dive times. We conclude that increased spleen size and O_2 carrying capacity are likely to be physiological adaptations for increased diving duration.

3. The evolutionary physiology of the diving response thus can be described in terms of the degree of development of adaptable vs conservative categories of diving characters: i.e., in terms of how these patterns change through time and how the patterns are lineage specific.

These principles supply us with a framwork for evaluating the evolution of hypoxia tolerance in humans and may allow evaluation of so-called 'true' physiological adaptations against hypoxia.

Human Response to Hypobaric Hypoxia

To this readership, the basic outlines of how our species defends against hypobaric hypoxia are well known and are clearly dependent upon the time available for the response. For convenience, we can categorize acute human hypoxia defense responses into several categories (see Winslow and Monge, 1987, for literature in this area):

1. increased ventilation mediated through the 0_2 sensing system in the carotid body (see Lahiri, 1984; 1996),
2. increased pulmonary vasoconstriction mediated through the 0_2 sensor in the pulmonary vasculature (Oelz et al, 1990; Anand and Chandrashekhar, 1990),
3. increased heart rate possibly with some redistribution of cardiac output (Richalet, 1990)*
4. increased perfusion especially of heart and brain, pH or modulator-mediated adjustment in Hb affinity for 0_2, and increased 0_2 extraction (see Winslow and Monge, 1987; Monge and Leon-Velarde, 1991),
5. peripheral tissue oxygen limitation during exercise, a reduction in $V0_2max$ (more notable in endurance trained athletes) and consequent augmentation of anaerobic metabolic pathways (higher plasma and muscle [lactate] values for any given exercise intensity - a special version of the Pasteur effect (see Hochachka et al, 1991; 1992)), and
6. increased catecholamine release and involvement in the regulation of several of the above processes (Richalet, 1990: 1997).

Taken together these adjustments momentarily compensate for the reduced availability of 0_2 in the inspired air. If the hypobaric hypoxia is not too severe, these mechanisms can fully compensate for reduced 0_2 supply. The cutoff point seems to be at about 3500 meters (see Richalet, 1990, for example), above which the compensation is incomplete and most unacclimated humans suffer various consquences (physiological defenses collapse into pathophysiology). That is why, from a purely physiological point of view, there is a need for developing backup acclimation (or acclimatization) defenses. Again, these are now well described in the literature and for lowland lineages can be summarized as follows:

1. hypoxic ventilatory response further exaggerated, implying an increased 0_2 affinity of the 0_2 sensing system in the carotid body (Lahiri, 1984; Biscard and Forster, 1996),
2. hypoxic pulmonary vasoconstriction maintained (Heath and Williams, 1981; Oelz et al, 1990) and may be further exaggerated, mediated by the pulmonary endothelium 0_2 sensor in an attempt to redistribute perfusion of the lung most advantageously,
3. heart rate, especially the maximum rate during exercise (Richalet, 1990), dampened as erythropoiesis increases the hematocrit and 0_2 carrying capacity of the blood (mediated by an 0_2 sensing system primarily in the kidney (Winslow and Monge, 1987)),
4. perfusion of heart and brain dampened to a new steady state also possible because of increased hematocrit (Severinhaus et al, 1966; Huang et al, 1987; Krasney et al, 1990; Richalet, 1990),
5. improved perfusion and oxygen supply to peripheral tissues, a partial recovery of $V0_2max$, and thus (Hochachka et al, 1991) reduced reliance during exercise on anaerobic augmentation of tissue energy production (lowering of [lactate] levels for a given level of exercise), and
6. a maintained catecholamine response (Richalet, 1990; 1997) involved in the regulation of several of the above processes.

Again, taken together these acclimation processes go a long way towards re-establishing physiological and metabolic homeostasis under hypobaric hypoxia. When, if ever, they are complete is a poorly explored area of research. Some kinds of acclimation response may continue on indefinitely. Monge's disease - a situation in which the hematocrit continues to rise throughout the lifetime of the individual - may be such a process gone somewhat out of control and thus referred to by Monge as a 'maladaptation' (see Monge and Leon-Velarde, 1991; Heath and Williams, 1981).

For lowlander Caucasians, the above acute and acclimatory processes constitute the only available defense arsenals against hypoxia. However, similar studies of highlander lineages (Quechuas and Aymaras from the Andes; Sherpas and Tibetans from the Himalayas) indicate some differences in both acute and acclimation responses. These indicate that over generational time, each of the general steps in the above hypoxia defense responses - from hypoxia sensing, through signal transduction pathways, to integrated metabolic and physiological responses - apparently can be further adjusted. For hypoxia tolerance in the human species, we do not have enough data of the type described for the diving model to do a quantitative

analysis of evolutionary pathways within our species. Nevertheless, when we extend the timeline of hypoxia defense through generations, we begin to see that (as in the diving model) many physiological traits involved in hypoxia tolerance are highly conservative while others are more malleable.

Most Physiological and Metabolic Characters in Humans Are Conservative

For example, the brain and CNS of low altitude and high altitude natives express the same absolute preference for glucose as a carbon and energy source. What is more, regional brain specializations and hence regional brain differences in glucose metabolic rates show the same patterns in both high and low altitude humans (see Hochachka et al, l995b, 1996a,b). Thus as 'physiological characters' both glucose preference and regional metabolic organization are highly conservative. Because we are dealing with comparisons within a single species (structures, functions, and control circuitries are necessarily built on the same biological plan), it is perhaps not surprising that most physiological and metabolic characters associated with hypoxia tolerance in humans display conservative aspects. Thus these deserve no further emphasis at this time. Instead, it is the malleable or 'adaptable' physiological and metabolic 'characters' that attract our greater interest.

Malleable or 'Adaptable' Traits in Human Hypoxia Tolerance

In contrast to the above kinds of features, relatively malleable traits are exposed when we compare the acute and acclimatory responses of Andean and Himalayan lineages to those of Caucasian lowlanders. Such comparative studies of highlander lineages indicate that

1. the hypoxic ventilatory drive is notably blunted, especially in Andean natives (Strohl and Beall, 1997), implying adjustments in the 0_2 affinity of the carotid body 0_2 sensing mechanism and in its regulation (Lahiri, 1984; 1996),
2. the hypoxic pulmonary vasoconstriction may be reduced (Heath and Williams, 1981), implying adjustments in the pulmonary vasculature 02 sensing system (Anand and Chandrasheckhar, 1992),
3. the lung diffusion capacity may be expanded to compensate for the hypobaric hypoxia of the environment (especially evident in Quechuas of the Andes (see Winslow and Monge, 1987),
4. a requirement for increased erythropoiesis may remain (in Andean natives) or may be de-emphasized (in Sherpas and Tibetans (Beall and Goldstein, 1990), but energy balance in different metabolic states (Hochachka et al, 1991) is maintained (presumably through perfusion adjustments in peripheral tissues and in part because of reduced oxidative capacities coordinated with reduced 0_2 demands),
5. heart rates during rest and exercise are lower, in part because the catecholamine response is blunted (see below) and in part because of increased preference for glucose as a fuel for the heart (Hochachka et al, 1996a) and reliance on carbohydrate during skeletal muscle work (Hochachka et al, 1991), thus improving the yield of ATP per mol of 0_2.
6. enzymic capacities of aerobic and anaerobic metabolic pathways in muscles are down-regulated (relative preponderance of slow twitch fibers) so that overall $V0_2max$ and anaerobic energy contributions are both relatively low (the higher the altitude, the lower the [lactate] for any given exercise level despite the hypoxia - a situation termed the 'lactate paradox' in the literature (Hochachka et al, 1991; 1992),
7. the overall performance strategy appears to be 'to go slowly but efficiently', and
8. the catecholamine response to hypoxia is relativley blunted even compared to hypoxia acclimated lowlanders (Richalet, 1997).

Are these true biological adaptations? Or are they merely inherited (ancestral) physiological responses in different lineages to the same environmental problem of hypobaric hypoxia?

Satisfying 'Adaptation' Criteria of Evolutionary Biologists

To adequately answer this question we need to recall the different ways in which this term is used by physiologists and by evolutionary biologists. As mentioned above, to physiologists a trait is frequently termed an 'adaptation' if its function improves chances of survival. Evolutionary biology is more demanding in its definition; in this discipline, a trait is termed an adaptation only (i) if it arises under natural selection, and/or (ii) if it is maintained by natural selection. Within the human species demonstrating these two properties (i.e. satisfying these two criteria) is no easy matter. Hence, indirect evidence is required to demonstrate

whether or not a complex physiological system such as 'hypoxia tolerance' is an adaptation. One such line of evidence involves demonstrating that the same or a similar physiological suite of traits arises in response to a given selective force more than once within the phylogenetic group under analysis. Based on the above analysis, the complex physiological system we need to evaluate can be summarized as 5 loosely linked functions:

1. Blunted hypoxic ventilatory response (carotid body 02 sensor)
2. Blunted hypoxic pulmonary vasoconstictor response (pulmonary vasculature 02 sensor),
3. Dampened heart rate and heart work (in part probably due to increased preference for carbohydrate carbon and energy source, and hence inccreased yield of ATP per mol 02 and in part due to increased hematocrit),
4. Decreased reliance upon anaerobic metabolic pathways in peripheral tissues (so called 'lactate' paradox), relative preponderance of slow twitch (ST) fibers in skeletal muscles with low oxidative capacities of all fiber types, and
5. Blunted catecholamine response to hypoxia, indicative of efficacy of above metabolic and physiological adjustments.

That these physiological traits are indeed at least loosely 'linked' is indicated by the fact that most of them are also found in humans adapted for endurance performance (see Hochachka, 1991). In endurance trained athletes these series of traits appear as high performance versions of those found in high altitude natives. Although the high performance features probably are a part of the explanation for greater percentage effects of hypoxia on $V0_2max$, an endurance athlete could be viewed as a high performance version of indigenous highlanders (such as Quechuas and Sherpas) and vice versa. Put another way, the biochemical and physiological organization of both indigenous highlanders and endurance athletes differ strikingly from the homologous organization in 'burst performance' individuals (where FT fibers form a larger percentage of skeletal muscle, exercise-induced plasma lactate concentrations can reach very high levels, and cardiovascular adjustments play as important a role in recovery from performance as they do during performance per se).

If these 5 loosely linked components compromise our species' 'solution' to the environmental 'problem' of hypobaric hypoxia, 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. A search for such evidence requires insight into the evolutionary pathways of our species. To this end, we constructed a simplified 'phylogenetic tree' for the human species from an indepth summary of human genetics and evolution by Cavalli-Sforza et al (1994). The main groups whose 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. If we assume that our species age is approximately 100,000 years, then a close examination of such information is highly instructive. First, it suggests that the last time Caucasians, Sherpas and Quechuas shared a common ancestor was over 50,000 years ago. Second, the last time the Himalayan highlanders (Sherpas and Tibetans) and the Andean highlanders (Quechuas and Aymaras) shared a common ancestor was in the range of 30,000 years ago - or about 1000-1500 generations ago. Third, despite this distant divergence of the latter two lineages, their metabolic and physiological responses to hypobaric hypoxia are similar. Fourth, many other lineages (including intermediate branches in the 'phylogenetic' tree of the human family) are known not to show these characteristics.

These phylogenetic data are consistent with two possible scenarios: (i) One possibility is that, with only modest differences, many similar metabolic and physiological 'solution' arose independently in these two lineages. If so, these comparisons satisfy at least one of the criteria of evolutionary biology and strongly support the conclusion that the above suite of physiological characters are defense adaptations against hypobaric hypoxia. (ii) A second possibility is that the above suite of physiological and metabolic traits represent the 'ancestral' condition, a view consistent with recent indications that the origins of our species occurred under conditions that were getting colder, drier, and higher (see Vrba et al, 1995). Over some 5000 generations of our species history, this condition was 'retained' in high altitude groups (Sherpas, Tibetans, Quechuas, Aymaras) and in groups selected for endurance performance. In the former, the ancestral physiological condition was 'low-capacity', fine-tuned for 'go slow but effficiently' under hypobaric hypoxia. In the latter groups, the ancestral physiological condition in relative terms became a 'high capacity' one, high capacity energy supply pathways being fine-tuned for the high capacity energy demand of sustained performance. In this scenario, the ancestral organization of our physiology was inherently very dependent upon 'aerobic' pathways, with relatively minor

development of, or reliance on, anaerobic metabolic systems.

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