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Elucidating Nature's Solutions to Heart, Lung, and Blood Diseases and Sleep Disorders

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Abstract

Evolution has provided a number of animal species with extraordinary phenotypes. Several of these phenotypes allow species to survive and thrive in environmental conditions that mimic disease states in humans. The study of evolved mechanisms that responsible for these phenotypes may provide insights into the basis of human disease and guide the design of new therapeutic approaches. Examples include species that tolerate acute or chronic hypoxemia like deep-diving mammals and high-altitude inhabitants, as well as those that hibernate and interrupt their development when exposed to adverse environments. The evolved traits exhibited by these animal species involve modifications of common biological pathways that affect metabolic regulation, organ function, antioxidant defenses, and oxygen transport.

In 2006, the National Heart, Lung, and Blood Institute (NHLBI) released a funding opportunity announcement to support studies that were designed to elucidate the natural molecular and cellular mechanisms of adaptation in species that tolerate extreme environmental conditions. The rationale for this funding opportunity is detailed in this Special Article, and the specific evolved mechanisms examined in the supported research are described. Also highlighted are past medical advances achieved through the study of animal species that have evolved extraordinary

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phenotypes as well as the expectations for new understanding of nature's solutions to heart, lung, blood, and sleep disorders through future research in this area.

Keywords

animal models; human disease; hibernation; hypoxia; deep-diving; high-altitude; diapause

Introduction

In 2007, cardiovascular, respiratory, and blood diseases accounted for over 1 million deaths and 43% of all deaths in the United States.[1] Of all diseases, heart disease is the leading cause of death, cerebrovascular disease is third (behind cancer), and chronic obstructive pulmonary disease (COPD) ranks fourth.[1] Despite a 12% decline in the number of deaths from heart, lung, and blood diseases from 1987 to 2007, the public health burden and economic costs remain high,[1, 2] and new effective interventions and treatments are needed. Innovative research approaches will improve understanding of the molecular and physiologic basis of human health and disease. One successful and often unexploited strategy in biomedical research is to examine naturally-occurring variations in animal species that are adapted to extreme environments. This approach follows August Krogh's principle that "for a large number of problems, there will be some animal of choice or a few such animals on which it can be most conveniently studied."[3] Krogh's principle is based on the observation that some organisms are particularly well-suited for studying specific problems that affect humans—*i.e.*, they have evolved phenotypes that either exemplify a phenomenon observed in humans, mimic essential aspects of a particular human disease, or permit a unique study approach. Krogh believed that these specialized adaptations could and should be exploited to solve specific biological problems.

One example of the application of Krogh's principle that advanced biomedical knowledge is the work performed on electric rays (*Torpedo californica*) and eels (*Electrophorus electricus*). These species were studied because they represented explicit examples of "animal electricity,"[4, 5] characterized by their specialized electric organs, which allowed them to generate electrical fields for communication, navigation, predation, and defense without shocking themselves. Work on electric rays and eels resulted in fundamental understanding of the molecular properties of acetylcholine receptors and membrane-bound ion channels.[6]

Venoms, another evolved strategy in some animal species for self-defense and seeking prey, initially piqued the interest of scientists because of their paralyzing potency.[7] The study of venom from sessile marine mollusks (genus *Conus*), resulted in the identification of several conotoxins, peptides with high affinities for human ion channels.[8] One of these peptides, ω-conotoxin MVIIA from *Conus magnus*, selectively blocks N-type voltage-gated Ca^{2+} channels, which control norepinephrine release from cardiac sympathetic nerves[9] and other neural pathways.[10] ω-Conotoxin MVIIA's synthetic equivalent, Ziconotide, is FDA-approved for treating neuropathic pain in cancer and AIDS patients,[11] and it has therapeutic potential for ischemic stroke[12] and other cardiovascular, respiratory, and blood diseases. Similarly, studies of venom from the American funnel web spider (*Agelenopsis aperta*) identified peptides with high affinities for ion channels in humans and other species.[13] One such peptide, ω-agatoxin IIA, specifically targets T-type and N-type voltage-gated Ca^{2+} channels, involved in the development of congestive heart failure, hypertension, and epilepsy.[14] Further studies with ω-agatoxin IIA may offer new therapeutic strategies for treating and preventing these diseases. The study of vampire bats (*Desmodus rotundus*) also supports Krogh's principle. Bites inflicted by these bats were known to bleed freely for

several hours after they finished feeding,[15] and biomedical investigators were interested in understanding how vampire bat saliva prevented blood coagulation in the host animal so that this knowledge might be used to improve therapeutic outcomes in people suffering from hypercoagulability syndromes and other cardiovascular disorders. These studies led to the characterization of plasminogen-activating proteins in vampire bat saliva,[16] which subsequently resulted in the development and Phase III clinical trial testing of Desmoteplase,[17] a new anticoagulant for stroke treatment.[18]

Krogh's principle has also been applied in research aimed at understanding the nervous system by using animal models with unique phenotypes. Giant axons from squid (*Loligo ssp*), were ideal for studies designed to elucidate the bases of neural activity because of their large physical size, which allowed the placement of recording electrodes across the membrane of a single neuron. This ability allowed the development of voltage-clamp techniques to measure changes in the membrane current underlying the development of an action potential, and it also spurred the development of experimental protocols to decipher the ionic bases of those currents. This pioneering work in giant squid axons led to the fundamental understanding of the ionic bases for resting and action potentials in nerves[19] and other excitable tissues, including heart.[20] Similarly, the investigation of sea slugs (genus *Aplysia*) was undertaken because they possessed a relatively small number of large nerve cells that were easily identified and could be individually mapped.[21, 22] Sea slugs exhibited a siphon-withdrawal response mediated by electrical synapses that allowed several neurons to fire simultaneously to permit a rapid reaction to danger.[23] The unique configuration of synapses in these species aided studies that were designed to elucidate the basis of memory.[21–23]

Comparative biology has also identified species with unique phenotypes that naturally mimic or accentuate aspects of human disease conditions. For example, "fainting goats," who suffered skeletal muscle rigidity and collapsed when startled, appeared to share symptoms of human congential myotonia, a neuromuscular disease characterized by slow muscle relaxation after contraction or electrical stimulation. Studies demonstrated that before stimulation, resting muscle fibers from this strain of goats had abnormal chloride channel kinetics due to ion channel protein mutations.[24] This finding, along with myotonic mice studies,[25] led to the prediction of the location of the Becker myotonia gene in humans[26] before the major chloride channel in mammalian skeletal muscle had been cloned.[27]

Burmese pythons (*Python molurus*) also mimic and accentuate aspects of human disease conditions with their unique responses after ingesting large prey. Fasting pythons have reduced stomach volume, decreased intestinal mass, and 'normal' heart volumes. However within 48–72 hours after feeding, pythons undergo massive remodeling of their entire digestive system and a 40% increase in heart mass.[28] Most mammalian models of hypertrophy, on the other hand, only exhibit modest myocardial hypertrophy (~10–20%) after weeks of stimulation.[29, 30] These responses in pythons allow them to serve as unique models of digestive physiology, metabolic regulation, and cardiac hypertrophy. Thus far, studies show that python heart growth is characterized by myocyte hypertrophy in the absence of cell proliferation through the activation of signaling pathways for fatty acid transport and oxidation.[31] A combination of fatty acids, identified in python plasma following ingestion of a large meal, promotes hypertrophy in mammalian cardiac myocytes.[31] This finding suggests the possibility that fatty acid supplementation might provide a new mechanism to modify cardiac gene expression and function and could be used to enhance cardiac performance in humans with cardiovascular disease.

Thus, in accordance with Krogh's principle, the understanding of human health and disease has been greatly aided by investigations of animal species with extraordinary evolved phenotypes. With this in mind, the National Heart, Lung, and Blood Institute (NHLBI) in 2006 released two funding opportunity announcements entitled "Elucidating Nature's Solutions to Heart, Lung, and Blood Diseases and Sleep Disorder Processes."[32, 33] The overall goal was to support "studies that elucidate the natural molecular and cellular adaptations of mammalian species to extreme environmental conditions that would rapidly evoke life-threatening cardiovascular or respiratory responses in other species, including humans" with the objective of identifying "new therapeutic targets to treat and prevent heart, lung, blood, and sleep disorders." This initiative underscored Krogh's principle by explicitly supporting the study of animal species with evolved mechanisms that facilitate their survival in conditions that mimicked or would normally result in human cardiovascular, respiratory, blood, and sleep disorders. The initiative encouraged comparative biologists, a group of investigators who had not traditionally been NIH-supported, to adapt their unique research models towards understanding the basis of human diseases with the hope of identifying new therapeutic targets. Seven studies (Table 1) were funded to examine the protective mechanisms evolved by hibernating mammals; fish that stop normal development (undergo diapause) under dehydrating conditions; high-altitude mice; and diving mammals. Although these animal species endure a diverse range of environmental challenges, they exhibit survival strategies that involve common pathways used by other species for metabolic regulation, organ function maintenance, antioxidant defenses, and O_2 transport.

Hibernators

Hibernation is a successful survival strategy employed by many species. For instance, mammalian hibernators in harsh winter conditions intolerable to other species and humans typically reduce their metabolism to ~1% of normal rates, decrease heart rate to ~5% of normal values, and suppress body temperatures to as low as −2°C without apparent harm.[34] Unlike non-hibernators and humans,[35] cold-climate hibernators selectively maintain vital organ function (*e.g.*, brain and heart) and are not susceptible to detrimental cardiovascular effects resulting from the low temperatures.[36–38] Distinguishing characteristics of the hibernator's heart that differ from that of the non-hibernator include the activation of signaling pathways elicited by ischemic preconditioning;[37, 39] changes in electrical properties;[40, 41] maintenance of Na^+/K^+ ion homeostasis;[42] and proteome alterations.[43] During arousal from hibernation, hibernators do not suffer tissue damage resulting from oxidative stress as experienced in non-hibernators.[44–46] Future research to determine the mechanisms that allow hibernators to survive dramatic seasonal changes will likely require elucidating the differential expression of mRNAs and proteins, as well as protein post-translational modifications, which distinguish summer-active animals from their winter-hibernating counterparts. Further studies will elucidate how non-hibernators can be protected from ischemia/reperfusion injury when they are induced to enter a reversible hibernation-like (*i.e.*, hypometabolic) state with hydrogen sulfide (H_2S), which acts as a vasodilator in the heart.[47, 48] Such a strategy might be applied to patients suffering out-of-hospital cardiac arrest or severe traumatic injury, permitting them to be placed in a state of medically-induced hibernation so that more time could be taken to transport them to an emergency department or hospital facility where advanced life-saving interventions, including surgery, would be initiated.[49] Understanding the strategies that allow hibernators to dramatically reduce their metabolic rates and tolerate cold temperatures may also result in development of better methods to preserve human organs prior to transplantation,[50, 51] improved resuscitation outcomes,[49] insight for protection against ischemia/reperfusion injury,[51, 52] and care for patients exposed to severe accidental hypothermia.[53]

Anoxia-Tolerant Species That Suspend Development in Adverse Conditions

Study of the evolved physiological mechanisms in species tolerant to O_2 deprivation may also contribute to the development of new therapeutic strategies to minimize morbidity and mortality in patients suffering out-of-hospital cardiac arrest and severe traumatic injury.[54] Anoxia- and hypoxia-tolerant species appear to share several characteristics (*e.g.*, higher hemoglobin (Hb)-O_2 saturation, lower metabolic rate, blood flow redistribution, and optimization of O_2 usage). One survival strategy adapted by animal species that normally endure prolonged O_2 deprivation is to enter diapause (*i.e.*, developmental arrest). Diapause occurs in a number of species, but it is most often observed in arthropods and egg-laying fish (*e.g.*, annual killifish *Austrofundulus limnaeus*).[55] The specific biochemical signaling pathways that regulate metabolic control and stress tolerance during diapause vary from organism to organism, but they share some common properties, which include a termination signal before development resumes and the accumulation of molecular chaperones (*i.e.*, heat shock proteins).[56] Other processes likely involved in diapause and in the regulation of biochemical pathways that exist in all animal species include metabolic control by adenosine monophosphate-activated protein kinase[57] and/or phosphoenolpyruvate carboxykinase,[58] as well as ROS/reactive nitrogen species signaling resulting in post-translational modifications that affect protein activity.[59] These pathways are being further investigated at the molecular level;[56] and insights gained from these studies will complement current knowledge of these processes in other animal species. Studies of mitochondrial physiology in diapausing species suggest that intrinsic regulation of electron transport and proton leak across the inner mitochondrial membrane may underlie anoxia tolerance,[60] a mechanism that might someday be triggered and employed in patients suffering chronic obstructive lung disease.

Elucidation of the mechanisms that initiate and maintain diapause has contributed to the understanding of early human embryonic growth, delayed embryo transplantation, and cryopreservation.[61, 62] In future work with anoxia-tolerant species, it will be important to determine how metabolic depression results in reduced energy consumption; identify what pathways support anaerobic metabolism; understand how mitochondrial physiology is regulated during anoxia/hypoxia; and explore the role of transcription factors/miRNA/epigenetics in anoxia tolerance.

High-Altitude Inhabitants

Animal species that have adapted to life at high altitudes also serve as models for elucidating the cellular and molecular mechanisms of tolerance to hypoxia-induced hypoxemia similar to conditions experienced by humans with anemia or COPD.[63, 64] For instance, deer mice that are native to altitudes >4000 meters have evolved elevated Hb-O_2 affinities relative to their lowland counterparts, which help to safeguard arterial O_2 saturation under hypoxic conditions.[65–67] The chronic hypoxia experienced by animal species that dwell at high altitude is similar to that observed in patients with conditions resulting in insufficient blood flow (*e.g.*, cerebrovascular hemorrhage, vascular occlusion, cardiac arrest, or bypass surgery) or respiratory dysfunction (*e.g.*, airway obstruction, asthma, emphysema, or lung dysfunction). Identifying and characterizing the molecular mechanisms of Hb adaptation to hypoxia, for instance, may guide the design of recombinant Hbs for use as O_2-carriers to enhance tissue O_2 supply in patients suffering hemorrhagic shock, hemolysis, and ischemic insult in humans.[68, 69] Further studies of adaptive changes in blood-O_2 transport at high altitude could also aid the development of new therapeutic interventions for high-altitude-induced sleep apnea[70] and various forms of chronic mountain sickness (CMS).[71, 72] The most prominent characteristic of CMS is excessive polycythemia, which leads to blood hyperviscosity, pulmonary hypertension, cerebral hypoperfusion, heart failure, and

death.[71, 72] Pharmacological interventions to reduce and prevent the CMS erythropoietic response are currently available,[73] but a safe and effective therapeutic approach to CMS for large-scale use remains lacking.[74] The challenge for future hypoxia research is to explore the cellular mechanisms and conditions that reconfigure an organ or cellular network into a hypometabolic state.

Diving Mammals

Diving mammals endure a variety of environmental stresses, and they have evolved physiological mechanisms that result in changes in respiratory drive, blood flow distribution, and heart rate to permit them to tolerate long periods of activity underwater without inhaling oxygen.[75, 76] Understanding these reflex responses and how they may be employed in patients has provided therapeutic interventions. For example, an induced “diving reflex” is a recognized therapeutic intervention useful in terminating supraventricular tachycardia, a sustained arrhythmia, in children.[77, 78] Increased understanding of the mechanisms that allow diving mammals to remain submerged for long durations and tolerate periods when arterial blood oxygen tension (pO_2)drops to anoxic levels in humans and land mammals might be useful in understanding, treating, and preventing some cardiovascular disorders and sleep disorders. During extended dives, coronary blood flow in seals may decrease to as low as ~10% of pre-dive values[79]—a level comparable to that observed in infarcted dog myocardium[80]—and arterial pO_2 may be less than 20 torr.[81] To prevent arterial blood pO_2 from falling, diving mammals dramatically elevate myoglobin content in their skeletal and cardiac muscle.[76] To manage reductions in coronary blood flow while diving, the seal heart relies largely on its large glycogen stores for fuel, resulting in lactate and H^+ ion accumulation.[79, 82] Upon resurfacing, the myocardium resumes using lactate as fuel and shows no evidence of ischemic dilation of the left ventricle or S-T segment elevation.[83] Elevated antioxidant levels in the blood and tissue of diving mammals may in part counter oxidative stress resulting from the rapid apnea to reoxygenation transition during diving.[84, 85] Understanding the mechanisms of how diving seals mobilize their high glycogen stores for fuel[82] could aid in identifying therapeutic targets treatment of glycogen storage diseases in humans, where defects in muscle glycogen synthesis or breakdown result in protein degradation, atrophy, hypertrophic cardiomyopathy, cardiomyocyte degeneration, and fibrosis.[86] Sleep apnea research might also benefit from the study of seals that are apneic for most of their sleep time with arterial pO_2 falling precipitously from a maximum of 108 torr to a minimum of 18 torr.[81, 87] Despite the increased prevalence and heightened awareness, obstructive sleep apnea (OSA) is still underdiagnosed and appears to be associated with diabetes, coronary heart disease, heart failure, and cardiac arrhythmias.[88–90] The number of patients with obese-hypoventilation syndrome (OHS), characterized by obesity, hypoventilation, and sleepiness, is rising.[91] OHS treatment options and long-term outcomes have been poorly studied,[91] and diving mammals may provide ideal animal models to better understand OSA and OHS.[92]

In addition to improving our understanding of sleep apnea, the study of seals might contribute to increased understanding of insulin resistance in people. Post-weaned elephant seal pups experience prolonged fasts of 8–12 weeks when unattended by their mothers,[93] and as a result, the pups become insulin resistant.[94, 95] Yet, elephant seals have evolved mechanisms that permit fasting pups to continue to appropriately normalize carbohydrate and blood glucose levels.[96, 97] Elucidation of these processes for glucose regulation in diving mammals could result in improved treatments for diabetes in people.[98]

Conclusions

Evolution has produced a diverse array of animal species with unique phenotypes that provide extraordinary models for understanding human disease processes and clues for the development of new, effective means for the early identification, treatment, and prevention of disease. In this way, these unique animal species fulfill Krogh's principle. The NHLBI-supported studies of animal species adapted to survive severe environmental conditions, which mimic or would result in human heart, lung, blood, and sleep disorders, are demonstrating that the mechanisms used by these species for metabolic regulation, organ function maintenance, antioxidant defenses, and O_2 transport have great potential for the development of new treatments for human disorders. These examples, along with the past successes of applying Krogh's Principle to the study of animal species with extraordinary phenotypes, underscore the power of employing nature's solutions to guide the development of novel therapies to treat and prevent human disease.

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Abbreviations

Ca^{2+}	calcium ion
CMS	chronic mountain disease
COPD	chronic obstructive pulmonary disease
°C	degrees Celsius
FDA	Food and Drug Administration
H^+	hydrogen ion
H_2S	hydrogen sulfide
Hb	hemoglobin
mRNA	messenger ribonucleic acid
miRNA	micro ribonucleic acid
NHLBI	National Heart, Lung, and Blood Institute
NIH	National Institutes of Health
NSF	National Science Foundation
O_2	oxygen
OHS	obesity-hypoventilation syndrome
OSA	obstructive sleep apnea
P_{O2}	partial pressure of oxygen
ROS	reactive oxygen species

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Table 1

Research Supported by NHLBI Funding Opportunity Announcements PAR-06-382 and PAR-07-102: Elucidating Nature's Solutions to Heart, Lung, and Blood Diseases and Sleep Disorder Processes.

Grant Number	Principal Investigator	Title	Institution
R01 HL087216	Jay Storz, Ph.D.	Mechanisms of Hemoglobin Adaptation to Hypoxia in High-altitude Rodents	University of Nebraska-Lincoln
R01 HL089049	Sandra Martin, Ph.D.	Biomarkers for the Two Phase Switches of Mammalian Hibernation	University of Colorado-Denver
R01 HL091763	Barbara Horwitz, Ph.D.	Mechanisms of Neuroprotection in the Nucleus Tractus Solitarius of Hibernators	University of California-Davis
R01 HL091767	Rudy Ortiz, Ph.D.	Mechanisms of Oxidative Stress and Inflammation during Prolonged Fasting and Sleep Apnea in a Naturally Adapted Mammal, the Northern Elephant Seal	University of California-Merced
R01 HL091781	Lin Yan, Ph.D.	Mechanisms of Intrinsic Cardioprotection in *Marmota momax*	University of Medicine and Dentistry of New Jersey
R01 HL092857	Shannon Bailey, Ph.D.	Mitochondrial Mechanisms of Hydrogen Sulfide Induced Suspended Animation	University of Alabama-Birmingham
R01 HL095454	Jason Podrabsky, Ph.D.	The Role of Phosphoenolpyruvate Carboxykinase and Reactive Oxygen Species in the Support of Anoxia Tolerance in Embryos of the Annual Killifish *Austrofundulus limnaeus*	Portland State University

Specific information about each of the grant awards listed may be found using the NIH Research Portfolio Online Reporting Tool (RePORT) available at http://www.projectreporter.nih.gov/reporter.cfm.