Fundamental questions about genes, inactivity, and chronic diseases

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Booth FW, Lees SJ. Fundamental questions about genes, inactivity, and chronic diseases. Physiol Genomics 28: 146–157, 2007. First published October 10, 2006; doi:10.1152/physiolgenomics.00174.2006.—Currently our society is faced with the challenge of understanding the biological basis for the epidemics of obesity and many chronic diseases, including Type 2 diabetes. Physical inactivity increases the relative risk of coronary artery disease by 45%, stroke by 60%, hypertension by 30%, and osteoporosis by 59%. Moreover, physical inactivity is cited as an actual cause of chronic disease by the US Centers of Disease Control. Physical activity was obligatory for survival for the Homo genus for hundreds of thousands of years. This review will present evidence that suggests that metabolic pathways selected during the evolution of the human genome are inevitably linked to physical activity. Furthermore, as with many other environmental interactions, cycles of physical activity and inactivity interact with genes resulting in a functional outcome appropriate for the environment. However, as humans are less physically active, there is a maladaptive response that leads to metabolic dysfunction and many chronic diseases. How and why these interactions occur are fundamental questions in biology. Finally, a perspective to future research in physical inactivity-gene interaction is presented. This information is necessary to provide the molecular evidence required to further promote the primary prevention of chronic diseases through physical activity, identify those molecules that will allow early disease detection, and provide society with the molecular information needed to counter the current strategy of adding physical inactivity into our lives.

Darwin; environment; environmental gene interactions; exercise; adaptation; preventive medicine; physical activity

THE TITLE OF THE CURRENT REVIEW ARTICLE (“Fundamental questions about genes, inactivity, and chronic diseases”) was that of the Edward F. Adolph Distinguished Lecture of the American Physiological Society Environmental and Exercise Physiology Section, which was given on April 3, 2006, at Experimental Biology 2006. The purpose of the lecture, and the current review, is to provide compelling information that will allow readers to consider whether physical inactivity should be ranked as a crucial biological question.

The Greek physician Hippocrates wrote 2,400 yr ago: “That which is used develops, and that which is not used wastes away... If there is any deficiency in food or exercise the body will fall sick.” Thus, a description of the biological and medical consequences of physical inactivity was observed early in written history.

In recent years, the clinical importance of Hippocrates’ early writings has been verified by a massive number of epidemiological publications. In brief, physical inactivity increases the relative risk of coronary artery disease by 45%, stroke by 60%, hypertension by 30%, colon cancer by 41%, breast cancer by 31%, Type 2 diabetes by 50%, and osteoporosis by 59% (54). Physical inactivity also increases overall mortality (67), obesity (95), falls in the elderly and/or the physical frail (45), total cholesterol (46), depression (95), and anxiety disorders. Furthermore, physical inactivity decreases mood, functional status in older adults, and serum HDL levels, which is associated with increased risk of cardiovascular disease (54). There is also some evidence that physical inactivity increases dementia (62) and harms school academic performance in children.

The increased prevalence of chronic diseases has influenced major scientific organizations to the next conclusions. The American Diabetes Association web site states, “Type 2 diabetes is associated with... physical inactivity...” (21, 34). The American Heart Association’s web site includes: “An inactive lifestyle is a risk factor for coronary heart disease...” (4, 34). The American Cancer Society web site claims, “Research shows that about one-third of all cancer deaths are related to dietary factors and lack of physical activity in adulthood” (3, 34). The Centers for Disease Control (CDC) has published that physical inactivity is an “actual” cause of many chronic diseases. Indeed, the extrapolation of the increased prevalence of chronic diseases by physical inactivity to approximate the number of deaths provides the estimate that 13% of all deaths in the US are premature due to physical inactivity (22). In summary, it is no longer debatable that physical inactivity is the “actual cause” of many chronic diseases. Therefore, based upon its high morbidity and mortality, physical inactivity should be considered as a higher ranking fundamental biological question.

GENES WERE SELECTED TO SUPPORT PHYSICAL ACTIVITY THAT WAS OBLIGATORY FOR SURVIVAL DURING THE EVOLUTION OF METABOLIC PATHWAYS

Adaptation

Adaptation to the environment is an essential component of Charles Darwin’s concept of the survival of gene pools. Reiterating Darwin, Edward F. Adolph, former President of the American Physiological Society (APS) and who the lecture from which this review originated, wrote in 1964: “Since, however, natural environments are not constant, those individuals with greater capacity to adapt may have selective advantages in survival and reproduction.”(2) A contemporary of Adolph, C. Ladd Prosser (80), also a former President of APS, defined “adaptation” in 1964 as broadly relating differences within and between organisms to environmental variation; for some biologists Prosser contended that adaptation refers to genetic fitting to the environment, while physiologists use adaptation to mean environmentally determined as well as genetically determined.
Organisms have at least three major strategies for adaptation at the protein level for survival. One strategy for adaptation to a new environment is to change DNA sequence (ranging from new genes to polymorphisms of existing genes). Polymorphisms are estimated to occur in no less than 5,000 yr (93). A second adaptive strategy to an environmental change is through epigenetic modifications. Epigenetic modifications are a process where the decoration of nucleotides, such as methylation of CpG islands, occurs; these modifications result in altered gene expression (adaptations to the environment). Importantly, epigenetic modifications result in changes in chromatin structure and not changes in nucleotide sequence. As such, this adaptive strategy can occur within a relatively short time frame. However, the current evidence involving methylation patterns that are incorporated into the germ line are transmitted to future generations is controversial (7, 30). The final adaptive strategy to an altered environment is to change the expression of existing genes in a period of hours, days, or weeks to produce changes in the levels of proteins or in protein catalytic activity at the biochemical level. Further description of adaptive increases in a nuclear-encoded gene for an electron transport protein (50), thereby demonstrating adaptation to increased cytochrome c protein in the gluteus muscle, shows that changes in gene expression in skeletal muscle with physical training do not result in similar changes in reproductive cells (gamete), allowing inheritance of the adaptation, but no direct data with training are available to prove the dogma. In summary, adaptive changes in DNA sequence, DNA epigenetic modification, and gene expression may provide a single organism with an adaptive advantage or disadvantage to the new environment. However, only changes in DNA sequence in reproductive cells are transferred to offspring.

Adaptations in Gene Expression Within the Lifespan of an Organism in Response to Changes in Physical Activity: Physical Activity-Gene Interactions

Only 40 yr ago it was unknown if physical activity could alter gene expression to produce biochemical adaptations. In the 1967 introduction of John Holloszy’s classic citation paper (50), he posed the possibility “that the differences between the respiratory enzyme levels of active and inactive muscles might be due not only to genetic differences but also to an adaptive process.” His results showed that treadmill running by rats for 12 wk to a final daily duration of 2 h/day resulted in an 86% increase in cytochrome c protein in the gluteus muscle, showing adaptive increases in a nuclear-encoded gene for an electron transport protein (50), thereby demonstrating adaptation to exercise at the biochemical level. Further description of activity-gene interaction occurred in 1984 with our demonstration of a pretranslational change in skeletal α-actin mRNA, which was decreased at the 7th day of inactivity produced by fixing the soleus muscle in a shortened position to cause atrophy (97a). Next in 1986, R. Sanders Williams and colleagues (101) reported that electrical stimulation of skeletal muscle for 21 days increased cytochrome b mRNA fivefold. In the middle 1990s, Carson et al. (19) used deletion mapping of the skeletal α-actin promoter in the anterior latissimus muscle of roosters undergoing stretched loading to find that serum response element 1 (SRE1) was a hypertrophy regulatory element. The migration of its binding protein, serum response factor in nuclear extracts to an oligonucleotide containing SRE1 was altered in electromobility shift assays (18), suggesting alteration of transcription factor-gene interaction. In 2002 with the advent of global gene profiling, Chen et al. (24) found that high-resistance contractions by skeletal muscle produced a profile of mRNA changes that was common to the growth pattern of proliferating cells exposed to serum. The next year, Pattison et al. (75) found, with the very conservative Bonferroni adjustment for multiple testing, a global profile of mRNA for inactivity that showed 385 probe sets, 203 increasing and 182 decreasing, which were significantly different at the 10th day of fixation of the soleus muscle in a shortened position to produce muscle atrophy, compared with control. The hundreds of changes in mRNA levels are a reflection of the number of genes responsive to physical inactivity (75). Taken together, the aforementioned studies, and many other uncited papers, establish that physical activity/inactivity interact with genes to produce adaptive changes in molecules that are precursors to changes in function.

Adaptations in Gene Structure Over Many Generations in Response to Changes in Physical Activity: Physical Activity-Gene Interactions

Neo-Darwinism would suggest that selective pressures over hundreds of thousands of years established DNA sequences for each species. Undoubtedly, physical activity as a means to actively acquire the needed elements for survival, as well as actively avoid danger, was one selective pressure. Those organisms not able to perform physical activity to acquire needed elements for survival were more likely to have their gene pools selected for extinction before reproductive age in a self-sufficient era. A limitation of the aforementioned idea is that rigorous empirical evidence demanded of many scientific studies can’t be obtained by recapitulating mammalian evolution in the laboratory. Instead our notion is that the metabolic pathways of the human genome were selected to optimize metabolism for daily physical activity; however, this notion must be based upon inferential reasoning using a recent model of experimental selection of physical activity (discussed next) and Darwinian medicine (discussed later).

**Experimental selection of physical activity.** Britton and Koch and coworkers (58, 59) used two-way artificial selection by selectively breeding those rats that could run the longest in a forced-treadmill test (termed “high-capacity runners”) and separately breeding those rats having the shortest running times (termed “low-capacity runners”), a process now reiterated for 15 generations with the high-capacity runners now able to run 10 times the distance in an endurance run test than the low-capacity animals.

After 11 generations of experimental selection, high-capacity rats compared with low-capacity rats (neither group was exercise trained), had 12% lower mean 24-h blood pressure and 48% greater maximal absolute relaxation of carotid arteries. High-capacity rats, never trained, also had twofold or greater peroxisome proliferative activated receptor-γ (PPAR-γ)
between 160 and 290 ml of O$_2$ per min; however, during physical activity these values can increase as much as 10-fold in athletes, suggesting that metabolic pathways likely were developmentally influenced by many factors, physical activity having the most.

In biochemical terms, oxygen is involved in both metabolic and respiratory processes. It is a substrate for all aerobic enzymatic reactions (35, 81). We suggest that the next logical step would be to include the idea that the energy demands and increased O$_2$ consumption of physical activity must have played an accompanying role in the selection of aerobic metabolic pathways. Indeed, O$_2$ flux increases 40-fold across both human legs during maximal exercise (17). It is thus reasonable to suggest that physical activity continued the selection of aerobic metabolic pathways after the rise in molecular O$_2$ initiated the process. The outcome was likely vital, allowing for a robust increase in O$_2$ flux that contributed to animals being able to move (i.e., physical activity) for survival.

Adaptations of genes to the environment during the hundreds of thousands of years that humans have been on Earth must have included allowing the body to undergo physical activity (short bursts; longer, endurance types; and strength activities) to facilitate survival, as physical activity was obligatory for gathering food, constructing shelter, and providing defense. Those adaptations that produce a new phenotype that makes the organism more fit for existence under the conditions of the new environment are more likely be selected. The classical gene-environment interaction during evolution can be used to describe how a change in environment can lead to maladaptations, including production of chronic diseases, as discussed next.

**Concept of Environmental-Gene Interaction**

The term environmental-gene interaction has, itself, evolved in meaning. Although Darwin did not know about DNA, he wrote that species either adapted to a new environment or became extinct, implying adaptation through selection of DNA sequences. Prosser (80) later wrote, “...the net effect of the new knowledge now emerging in physiological genetics is to provide a cellular explanation for the adaptive interactions between the environment and the organism.” Prosser’s concept of physiological genetics in 1964 was prophetic as the term “physiological genomics” first appeared in a title of an article in 1998 (96). The following year, Cowley (29) defined physiological genomics as including efforts to link genes to cell replication, development, metabolic function, intracellular signaling pathways, signal transduction, tissue and organ function, and the ultimate goal, whole organism functioning, and the first issue of this journal appeared. It is really remarkable that Prosser’s vision of physiological genetics came so soon (1964) after Watson and Crick (97) published their double helix model of DNA in 1953. Arthur Beaudet (8) elegantly explained in the 1990s the concept of environmental-gene interaction to disease with his statement: “...any given individual will inherit a particular combination of disease susceptibility genes that produces some relative risk that may combine with an environmental component to cross a threshold of biological significance such that the individual is affected with overt clinical disease.” In Beaudet’s definition, we suggest that substitution of the term “physical inactivity” for “environmental” can be made as physical inactivity is one of the environmental components inferred in the quotation. Our modification of Beaudet’s concept of environmental-gene interaction includes the notion that each individual has their own “array” of disease susceptibility genes that will interact with physical inactivity to produce maladaptive changes in gene expression that often pass a clinical threshold into a chronic disease phenotype.

Whereas the environment selected gene sequences during the hundreds of thousands of years of evolution, the current environment affects how the “stone age” genes express proteins. Today, however, we are not as physically active as our “stone age” ancestors, or even our ancestors from 100 yr ago.
The time frame for the current environment of physical inactivity is too short to have selected polymorphisms beneficial to physical inactivity. Rather, in the past few decades, physical inactivity has been shown to alter the expression of existing genes, producing maladaptations (see discussion at the start of this article on disease prevalence). As mentioned at the beginning of this review, anecdotal evidence of physical inactivity-gene interaction was noted as early as Hippocrates; however, evidence to support physical activity/inactivity interaction with genes is only of recent vintage.

Change in Environment Without Change in “Stone Age” Genes

Self-sufficiency is defined sociologically as each human or small group of humans being responsible for their own food, defense, and shelter. Very simplistically we conceptualize that caloric need drove physical activity in the self-sufficient period. The procurement of food and shelter was essential for survival. If one survived to reproductive age, then one stood a greater chance of successfully passing their genes to the next generation. In contrast, those who were physically unable to find food in the self-sufficient period were more likely to have their gene pool selected for extinction. The self-sufficient period for the Homo genus essentially began ~2 million yr before present, during the transition from Australopithecus to Homo erectus. When the self-sufficient period ends is obviously up for debate; however, whether it was at the beginning of the industrial revolution or 100 yr ago is negligible since the previously up for debate; however, whether it was at the beginning of the industrial revolution or 100 yr ago is negligible since the self-sufficient period makes up ~99.99% of Homo genus. Non-self-sufficiency is defined here as humans obtaining a constant supply of food until reproductive age through a distribution network composed generally of farmers to transporters to sellers to buyers to consumers. This major sociological advance engineered a significant portion of physical inactivity into daily living.

The success of engineering physical inactivity into daily living is witnessed by the fact that more than 50% of American adults do not get enough physical activity to provide health benefits and 25% of adults are not active at all in their leisure time (20). Importantly, the same trend occurs in those just reaching reproductive age. Approximately 2/3 of students in grades 9 through 12 in the US do not meet minimum physical activity requirements (32). It is obvious that the vast majority of children and adolescents in developed nations do not need to be physically active for survival; however, there is a striking lack of leisure physical activity in the today’s youth.

Coupled to the remarkable development of labor-saving devices that engineered physical inactivity into daily living are the spectacular advances in medicine, particularly in the field of infectious disease. The beneficial outcome is that most infant diseases have been eradicated and infant mortality during the first year of life has been markedly reduced. From US Census Bureau records, we estimate that for every 1,000 births in the US today, 987 reach 19 yr of age. Therefore, the overwhelming majority of children born in the US now reach 19 yr of age. The low death rate up to reproductive age is evolutionary significant because Darwin’s doctrine implies that there is a selection of the fittest to due to the pressures of a new environment. However, in today’s society our youth do not have to procure food and shelter. Furthermore, due to advances in modern medicine, the majority of deaths between the ages 1–19 yr are mainly due to accidents. Therefore, our society has largely removed selective pressures of survival on the genome.

**How and Why Physical Inactivity Interacts with “Stone-Age” Genes Causing a Maladaptive Response**

How Does the Body Maladapt to Inactivity?

Physical inactivity and hereditary risk for Type 2 diabetes. The Harvard Nurse’s study reported that women with parents having Type 2 diabetes had a higher relative risk of Type 2 diabetes themselves than did women whose parents did not have Type 2 diabetes (52) (Fig. 1). These findings illustrate that there is a hereditary risk (disease susceptibility genes) involved with this disease. Moreover, these data also reveal a physical inactivity interaction with Type 2 diabetes susceptibility. For the women whose parents had Type 2 diabetes, the 20% most inactive had a 65% greater risk of diabetes than the quintile of women who were the most active (Fig. 1). In similar manner, for the women whose parents did not have Type 2 diabetes, the 20% most inactive had twice the risk of diabetes than the most active quintile. The fact that inactivity increases the prevalence of diabetes in women both with and without parents with diabetes reveals an actual epidemiological example of environmental/physical inactivity-gene interaction leading to a chronic disease.

**Predisposing gene for Type 2 diabetes and lack of physical activity.** Four variants in a >10-kb region that includes the P2 promoter of the hepatocyte nuclear factor 4a (HNF-4A) gene are associated with Type 2 diabetes (85). Francis Collins indicates that this disease predisposing polymorphism alone can’t cause Type 2 diabetes; rather the presence of “other, yet-to-be identified, genetic susceptibility factors, together with certain environmental influences such as obesity and/or lack of physical exercise” must occur (72). This interpretation reveals...
Physical inactivity as a potential vital environmental trigger for disease susceptibility and supports our proposition that physical inactivity is a basic biological question.

**Systemic changes.** As mentioned at the start of this review, Hippocrates had already recognized that the body wastes away and falls sick when physically inactive. A current example of the physiological adaptations to physical inactivity is when healthy humans undergo continuous bed rest or go into the microgravity environment of space. In response to excessive inactivity, they exhibit a rapid loss of tissue mass and disruption of normal function in many cells and tissues. Within weeks of the onset of continuous bed rest by humans, numerous adaptations occur, including −25% decreases in maximal stroke volume, maximal cardiac output, and peak consumption of O₂ during maximal aerobic exercise (83). Orthostatic intolerance occurs due to attenuated baroreflex-mediated sympathoexcitation in response to incremental declines in arterial blood pressures (39). Bones lose mass at 10 times their normal rate (88). Skeletal muscles become weaker with less endurance for light physical effort (1). In addition, metabolic pathways adapt to inactivity by decreasing mitochondrial concentration in skeletal muscles (38), lowering the capacity to oxidize fatty acids. Whole body insulin sensitivity declines within the first 3 days of inactivity, whether it is bed rest (65, 87) or active individuals stopping daily exercise (15, 73). Constipation ensues (14). Deep vein thrombosis can occur within a time frame as short as an international flight with possible pulmonary thromboembolism in susceptible individuals (26). In summary, the body’s adaptations to physical inactivity result in a loss of many structural and physiological processes, which often lead to unhealthy, in some cases life-threatening, conditions. Biological curiosity, alone, should drive inquiry into why the body constructed in a manner to so adversely adapt to physical inactivity. Therefore, the marked physiological maladaptations to physical inactivity lead us to ask how does the body maladapt to physical inactivity? And why was the body selected during the last hundreds of thousands of years to respond so adversely in function and health to physical inactivity? These are fundamental questions of biology. Unfortunately relatively little is known on the fundamental question of inactivity, some of which are briefly described next.

**Metabolic changes.** Physical activity is not simply one side of the energy balance equation. In fact, physical activity interacts with a plethora of metabolic and health-related functions, independently of energy balance. One apparent maladaptation to physical inactivity is the loss in the density of skeletal muscle mitochondria. In 1977, we reported that skeletal muscle mitochondria are rapidly lost when rats cease running each day. After a 2-day lag period during which the training-induced increase in skeletal muscle mitochondria is maintained during inactivity (12, 61), there is a loss cytochrome c concentration and citrate synthase activity; both are markers of mitochondrial density. The rapidity with which these changes occur is such that one-half of the gain in mitochondrial marker with training is lost between days 2 and 9 of no exercise in those rats formerly running 2 h each day (12). Similar findings were next reported in humans; cytochrome oxidase activity (a marker of electron transport chain capacity in mitochondria) increased 35% in the human quadriceps femoris muscle after 8 wk of aerobic training but returned to sedentary level only 2 wk after ceasing the aerobic exercise (49). These human and animal studies both demonstrate rapid declines in mitochondrial density when physical activity is ended. Reduced mitochondrial function in skeletal muscles is now believed to play some causal role in Type 2 diabetic subjects, as initially reported by Kelley’s group in the 1990s. For example, carnitine palmitoyl transferase (rate-limiting enzyme in the transfer of long-chain fatty acyl CoA across the inner mitochondrial membrane) and citrate synthase activities in vastus lateralis muscle homogenates were found to be progressively lower with each incremental increase in human visceral fat (27). They also found that the ratio of hexokinase/citrate synthase activities in the vastus lateralis muscle was negatively correlated to insulin sensitivity (86). Furthermore, obese subjects have an impaired capacity to oxidize fatty acids in legs (56) or whole body (89). Overall, mitochondrial densities are lower with physical inactivity in healthy subjects and patients with obesity/Type 2 diabetes, supporting the hypothesis that physical inactivity may play a role in triggering metabolic dysfunction.

In 1980, we showed that the capacity of isolated subsarcolemmal mitochondria from rat gastrocnemius muscles to produce ATP during state 3 respiration increased 47% after 12–16 wk of running 1 h/day and decreased 37% after 2 days of hindlimb immobilization in the shortened position in rats (60). Recently, Kelley’s group found a similar observation in humans. The electron transport chain activity in the subsarcolemmal mitochondrial fraction was approximately sevenfold lower in Type 2 diabetes and about threefold less in obesity compared with lean subjects (82). We believe that physical inactivity reduces subsarcolemmal mitochondria and may thus play a role in these clinical conditions.

**Why Does the Body Maladapt to Inactivity?**

**Energy storage and flux.** A general answer to the question is that ancient metabolic and signaling pathways require a minimal threshold of transient flux between energy expenditure and storage and that chronic physical inactivity falls below this threshold (Fig. 2). The frequency of cycling of these transient fluxes in physically active individuals may be as often as one to multiple times per day. Upon physical inactivity, some substrates and products from these pathways become dormant because transient metabolic fluxes are reduced. For example, both “aerobically trained” individuals and obese/Type 2 diabetic individuals have higher intramuscular levels of triacylglycerides; however, the former (“aerobically trained”) have high insulin sensitivity and the latter (sedentary obese/Type 2 diabetic) have low insulin sensitivity (44). Nonetheless, some still contend that lipid accumulation in skeletal muscle causes insulin resistance (77). On the other hand, van Loon and Goodpaster (91) propose that the metabolic paradox of inverse insulin sensitivity could be explained by the fact that it is not the size of the intramuscular triacylglyceride pool but, rather, a lack of its turnover in the physically inactive individual. Inactivity produces an imbalance among free-fatty acid uptake, intramuscular triacylglyceride storage, and free-fatty acid oxidation, which results in the accumulation of triacylglyceride; if the accumulated triacylglyceride does not turn over its byproducts (fatty acid metabolites), the by-products may decrease insulin sensitivity (47, 91).
There are at least three ways to test the transient flux hypothesis. Briefly, these approaches are: 1) experimentally reconstruct what might have happened during evolution; 2) employ Darwinian medicine to speculate on function; and 3) take physically active subjects and impose sedentary lifestyle to mimic the most recent 100 yr. Each will be considered in turn. The first approach would be to reconstruct evolution in the laboratory starting with anaerobic organisms without atmospheric O$_2$, slowing raising O$_2$, and observing higher-order mammals evolve over the next 2 billion yr. Clearly, this experiment is not feasible. A second approach is Darwinian medicine. Darwinian medicine is defined as providing some speculations using evolutionary explanations of vulnerabilities to disease (71, 99), with the aim to develop more specific hypotheses that might be tested. Since evolution can’t be recapitulated to humans and since physical inactivity is an “actual” cause of chronic diseases (68), evolutionary speculations will be made next. The third potential approach is to develop models of physical inactivity, which will be also considered later in this review.

Adaptations to short periods (hours) of physical inactivity appear to be a normal response to daily living. It is important to note that we consider adaptation to short-term physical inactivity as an integral aspect of transient flux between energy expenditure and storage. In contrast, maladaptation to prolonged/chronic (days/weeks) physical inactivity results in a disadvantageous outcome as a result of dropping below a minimum threshold of transient flux between energy expenditure and storage (Fig. 2). Three examples of adaptation to physical inactivity will be given. All three depend on the same set of premises, described next. First, neurons normally only oxidize glucose for ATP; however, with prolonged starvation neurons adapt to be able to oxidize ketone bodies (36). Second, the human body was selected to store only enough metabolizable carbohydrate to fuel less than one day’s resting energy requirements (16). The speculated reason for limited stores of glucose in the body is that glycogen has water molecules attached to it so that it weighs more than an equivalent number of calories stored as triacylglyceride (98). It is feasible to speculate that it is more efficient to carry a lower body weight; therefore, it costs less energy to carry a given number of stored calories as fat than glycogen when physically active (66). In summary, because the storage of whole body glucose for the brain the limited, a principle of Darwinian medicine has been employed to hypothesize that genes might have been selected for conserving glucose.

**Conservation of Glucose I**

**Rapid increases and decreases in insulin sensitivity.** In the absence of food, the body conserves its limited, internal supply of glucose by two alterations in insulin signaling: 1) lowering the level of blood insulin and 2) suppressing insulin sensitivity. The level of insulin sensitivity is independently regulated by each skeletal muscle. Decreases in insulin sensitivity shift the insulin dose-response curve to the right, i.e., a decreased number of glucose molecules enter a muscle cell (decreased glucose uptake) for any given level of blood insulin.

**FOOD.** The rise in postabsorptive blood glucose is regulated mainly through insulin signaling. Increased blood insulin stimulates insulin receptors to signal the translocation of glucose transporter 4 (GLUT4) to the plasmalemma. Human skeletal muscle accounts for 85% of whole body blood glucose uptake (31); in contrast, when food is deficient, blood insulin is low and therefore, insulin-stimulated glucose uptake into human skeletal muscle declines to 14% of the glucose removed from the blood (6).

**PHYSICAL ACTIVITY/INACTIVITY.** Skeletal muscle contraction locally regulates glucose uptake into each skeletal muscle. During muscle contraction, the process of insulin-mediated glucose uptake is largely overridden and GLUT4 translocation to the plasmalemma is insulin independent (51). As the acute effect of exercise on glucose transport declines, there is a subsequent increase in insulin sensitivity (51). Once local glycogen stores in the recovering skeletal muscle become replenished, insulin sensitivity decreases, which conserves glucose for vital central nervous system function (51). Speculation per Darwinian medicine is that since for hundreds of thousands of years humans have experienced short, intense bursts of daily physical activity (37), the physiology has been selected to conserve glucose.
of years food availability was uncertain/sporadic and human glucose stores are limited, a selective pressure led to the development of glucose conservation systems that respond to inactivity/activity levels. Indeed, the enhanced whole body insulin sensitivity of physically active humans returns from its elevated levels to sedentary values by 38–60 h in humans and rats (15, 61, 73).

We speculate that survival in a self-sufficient environment in the past hundreds of thousands of years not only selected today’s metabolic pathways but also optimized signaling mechanisms that allows cycling of these pathways, such as GLUT4 and insulin sensitivity, to coincide to fluctuations in food availability and physical activity. We have previously hypothesized that the combination of continuous food abundance and a sedentary lifestyle results in metabolic derangements because of the absence of cycling with the lack of physical activity, i.e., a stalling of the evolutionarily programmed metabolic cycles that were selected to support cycles of feast and famine and of physical activity and rest (23). A fundamental question has to be what are the critical changes in gene expression in response to physical inactivity that lead to alterations in the cycling of insulin sensitivity?

Conservation of Glucose II

Gluconeogenesis from muscle amino acids. Skeletal muscle atrophies within days of starvation. Why would it be advantageous to the organism for skeletal muscles to atrophy in the lack of caloric intake? Amino acids released from skeletal muscle can be utilized as a substrate for gluconeogenesis to produce glucose. Genes that code for the key enzymes that allow gluconeogenesis to utilize skeletal muscle amino acids were likely selected as it is advantageous to make use of the vast stores available in skeletal muscle. As a result, humans have evolved to utilize amino acids in skeletal muscles as a source of endogenous glucose when external sources of glucose from food were absent. To resupply amino acids for another round of atrophy, in anticipation of subsequent food deficiencies, skeletal muscle regrowth (hypertrophy) is essential. Consequently, multiple cycles of atrophy and hypertrophy might occur within a life span.

Lack of food without exercise. The extensive work of Wolfe (103) implies the existence of multiple minicycles of amino acid efflux and influx for skeletal muscles occurring with cycling of meals/snacks within a day. Between meals, amino acids are in a net efflux from human skeletal muscle (10), supporting the notion that genes may have been selected so that skeletal muscle amino acids could rapidly be released into the blood to maintain blood glucose levels between meals. Amino acids released from muscle supply substrate for liver gluconeogenesis to booster glucose supply. Conversely, feeding transiently stimulates muscle protein synthesis sufficiently to tip amino acid balance to a net influx (78).

Activity and inactivity with nutrition. While resistance exercise (such as weight lifting) increases muscle protein synthesis in fasting, protein breakdown is also increased so that a net amino efflux from the muscle exists (79). Nutritional intake is required for resistance exercise to be anabolic (103). When combined, resistance exercise and feeding synergistically interact to result in a greater protein anabolism than with feeding alone (78). The feeding- and exercise-induced stimulation of anabolism, if repeated sufficient times, results in muscle hypertrophy. Interestingly, only essential amino acids, particularly leucine, stimulate muscle protein synthesis (57). As the human body does not synthesize essential amino acids, an exogenous source of leucine is necessary to “prime” amino acids to be partitioned into muscle protein. One speculation could be that the selection of leucine is like a safety mechanism, acting as a signal that an exogenous source of amino acids was ingested.

As mentioned earlier in this review, bed rest causes skeletal muscle atrophy. However, supplementation of diet with essential amino acids and carbohydrate [experimental protocol (EXP)] in healthy young subjects maintained lean leg mass (as determined by dual energy x-ray absorptiometry) during 28 days of bed rest, whereas the bed rest group without the supplementation [control (CON)] lost lean leg mass (37, 74). Furthermore, even though both groups lost muscle strength, the EXP group maintained a higher percentage of pre-bed rest strength than the CON group (37, 74). In summary then, we speculate the gene expression patterns underlying atrophy (e.g., limb immobilization and bed rest) and hypertrophy (e.g., resistance training) had the purpose of providing a selective advantage in the self-sufficient era to allow the massive withdrawal of amino acids for glucose (atrophy) and deposit amino acids (hypertrophy) for future withdrawals.

Conservation of Glucose III

High levels of enzymes for oxidation of fatty acids. Chris- tensen and Hansen (25) first demonstrated in 1939, later replicated in the 1960s (84), that aerobically trained individuals derive a greater percentage of their energy from oxidation of fatty acids and less from carbohydrate than do untrained individuals at a given submaximal work load. Increases in enzymes of fatty acid oxidation in trained skeletal muscle underlie a part of their greater utilization of fat as an energy source during exercise, thus sparing of carbohydrate as an energy source during physical activity (69). Likely, individuals in the self-sufficient period were similar to today’s aerobically trained individual in being able to spare glucose usage during physical activity by having a greater oxidation of fat, conserving glucose in case food suddenly became unavailable. The lack of physical activity today produces maladaptations found in obese and Type 2 diabetic skeletal muscles: low capacity to oxidize fat, low mitochondrial density, and metabolic inflexibility (55).

ROADMAP: ALTER GENE EXPRESSION VIA BIOTECHNOLOGY OR LIFESTYLE?

Why is Physiological Genomics Needed to Identify Genes Interacting With Physical Inactivity? Why not Just Perform Behavioral Research Aimed at Modifying Physical Activity Levels?

One answer is that we already have adequate guidelines for the amount of exercise that will provide health benefits to the vast majority of society. Furthermore, most individuals know that physical activity is good for them. Despite this, approximately two-thirds of adults in the US do not meet the US Surgeon General’s recommendation for daily physical activity. Therefore, additional approaches are required to buttress hu-
man behavior to prevent inactive lifestyles, some of which are described next. First, it will be necessary to know which genes nature selected to meet the physically active environment during the hundreds of thousands of years that humans were self-sufficient; otherwise all true functions of genes will never be known. For example, understanding how and why physical inactivity produces low insulin sensitivity will elucidate a cause of Type 2 diabetes (47). Second, a gene function can’t be actually classified as “dysfunctional” if it is compared with the wrong reference point. Cessation of aerobic training for 2 days in rats (61) and for 6 days in humans (94) lowers skeletal muscle GLUT4 protein to sedentary levels. Thus, inactivity causes a predisposition to Type 2 diabetes by lowering muscle GLUT4 protein. However, it is often contended that skeletal muscle GLUT4 is not altered by Type 2 diabetes (5, 40, 42, 76), but these comparisons to sedentary subjects provide a different answer than if they had been made to physically active subjects. Third, molecules drive policies for better health. For example, the recent US Surgeon General’s report on “The Health Consequences of Involuntary Exposure to Tobacco Smoke” (90) uses molecules (formaldehyde, benzene, vinyl chloride, arsenic, ammonia, and hydrogen cyanide are in secondhand smoke) as evidence to conclude: “Secondhand smoke exposure causes disease and premature death in children and adults who do not smoke.” If physiological genomics is to accept the CDC’s recognition that physical inactivity is an “actual cause” of disease, then molecules responsible for the “actual cause” need to be identified. Fourth, molecules triggering disease from physical inactivity could in the future be used as early prognostic markers, which will be beneficial for earlier clinical intervention and potentially primary prevention.

How can the Maladaptations to Physical Inactivity be Engineered out of Daily Living?

The situation to which many humans are now fortunate to find themselves has been described by Eaton et al. (33), whereby our genes have been passed on to us from the “stone age,” whereas our society has developed to the “space age.” The result is a disruption of the homeostatic mechanisms optimized over hundreds of thousands of years due to our current “space age” environment. To solve the discord, the question is posed: can biotechnology make “stone age” genes modern, or do “stone age” genes need to be re-exposed to the milieu of the “stone age” environment? The former possibility will be considered first.

Alter the “stone age” gene by modern biotechnology. Remarkable scientific progress now allows the cloning of animals, gene therapy, and pharmacogenetics (drugs designed to address specific genes or DNA mutations). Why not just apply biotechnology to allow all humans to be sedentary? Currently, it is not possible to modify “stone age” genes such that they do not require physical activity for normal expression and optimal health. The biotechnological possibilities and their shortcomings are:

CLONING. The authors believe that cloning humans is not a viable alternative because of the ethical and legal considerations; furthermore, this strategy does not cure humans that are already living.

GENE THERAPY. The authors also believe that while gene therapy is a viable possibility for monogenic diseases such as Duchenne’s muscular dystrophy, gene therapy seems less feasible for polygenic disorders such as many chronic diseases and even much less likely for multiple chronic diseases like the cardiometabolic syndrome. Moreover, since inactivity affects multiple chronic diseases, such as coronary artery disease, stroke, hypertension, colon cancer, breast cancer, Type 2 diabetes, osteoporosis, and dementia, the vast numbers of genes required for gene therapy does not seem feasible. In addition, it is unlikely that society can afford the cost of treating 6 billion humans with multiple gene therapies.

EXERCISE PILLS. The Director of the National Human Genome Research Institute, Francis Collins, and colleagues (28) contend, “Genomics holds the promise of ‘individualized medicine,’ tailoring prescribing practices and management of patients to each person’s genetic profile. These revelations should also lead us to develop and target drugs in a rational fashion to genes, protein pathways, and networks shown to be involved in primary disease pathogenesis.” However, Williams and Kraus (100) present the limitation that any exercise pill only will partly substitute for all health benefits: “Further advances in our understanding of signaling mechanisms that govern activity-dependent gene regulation in skeletal muscle could lead to drugs, gene therapy, or devices that can, at least in part, substitute for daily exercise.” To replace all of the health benefits of exercise, one pill would have to improve memory, produce physiological cardiac hypertrophy with its associated increased resting and maximal stroke volumes, increase nitric oxide levels in vascular endothelial cells, increase bone strength, improve strength of skeletal muscle, enhance the immune system, lower TNF-α, increase insulin sensitivity, convert muscle fibers to the energy-saving type I fibers, increase mitochondrial density in skeletal muscle, lower postprandial serum triacylglyceride levels, and increase capillarization of skeletal muscle. A pill to mimic even one of the above is often not available, much less for all in the same pill. The challenge of unraveling complex etiologies and understanding their differences in healthy individuals of apparently similar phenotype is said to be daunting (8, 70). Thus, “exercise pill” is a scientific misnomer because there may never be one pill to replace all the health benefits of exercise, as stated by Williams and Kraus (100). Furthermore, it will be unethical to use the term “exercise pill” because patients using the pill might stop all physical activity so the exercise benefits not protected by the pill could lead to pathology and chronic diseases not counteracted by such a monolithic pill. Some evidence to the effectiveness of medication vs. lifestyle can be obtained from the results of the US Diabetes Prevention Program. The lifestyle intervention (weight loss, diet, and physical activity) had a greater effect than metformin on glycosylated hemoglobin, which reflects the mean blood glucose concentration over the preceding 6–8 wk. Furthermore, a larger proportion of participants in the lifestyle-intervention group had normal postload glucose values at follow-up. The incidence of Type 2 diabetes was reduced by 58% with the lifestyle intervention and by 31% with metformin, compared with placebo. Therefore, the lifestyle intervention group was about twice as effective as the drug.

How will knowledge of functional genomics be used? The information gained from functional genomics should be used for both primary prevention and pharmacological treatment. While the above data indicate that lifestyle intervention is more...
effective than drugs for the prevention of lifestyle diseases, pharmacological treatments are needed for those unable to exercise, such as paraplegics, the frail, or healthy with medical conditions preventing physical activity. Importantly, Williams and Kraus (100) indicate that while drugs may help ameliorate certain pathologies associated with inactivity, as mentioned earlier, it will be impossible to approach all the health benefits of physical activity with drugs. Therefore, drugs will never be a plausible, complete substitute for those individuals who can undertake a physically active lifestyle.

Revert to a “stone age” environment for health. Pragmatically, the best solution should be to accept physical activity as an integral aspect of our lives. The numbers of gene-environment interactions that occur with physical activity that are necessary for optimal health are astonishing. Here we apply the principle of Ockham’s Razor, which translates as “entities should not be multiplied unnecessarily.” In the case of chronic diseases caused by physical inactivity, we need not complicate matters by producing separate drugs for each of the benefits afforded by physical activity when physical activity is already the answer. Our time and effort would be better spent determining how and why physical activity causes the body to adapt rapidly to intermittent inactivity and maladapts to prolonged inactivity as a means to provide molecules to promote public health.

Roadmap for Physical Inactivity Research

Models of physical inactivity. The most appropriate model to mimic changes in gene expression when a sedentary lifestyle is imposed to force physically active subjects to abstain from exercise and become sedentary (13). Exercise physiology has studied this model before, termed “detraining.” A study utilizing a human model was mentioned previously wherein aerobically trained humans were not permitted to exercise and their enhanced whole body insulin sensitivity returned to sedentary levels by 38 or 60 h (15, 73). Hearn (48) first described detraining in rats in 1965. We have employed his model to extend the human studies by showing a return of enhanced insulin sensitivity in the epitrochlearis muscle to sedentary values at the 53rd h of detraining (61). Our model further has been used to show that inactivity, alone, can produce enlargements in intra-abdominal fat stores (63).

Potential directions. One possible approach to further our understanding on physical inactivity-gene interaction is as follows: Initially, those genes that cause pathology during prolonged/chronic physical inactivity need to be identified. It is likely that inactivity genes will form a subpopulation of genes predisposing an individual to chronic diseases. The role, if any, of newly identified genes in a particular disease state will need to be determined since physical inactivity increases the relative risk of multiple chronic diseases (11, 22, 54), as enumerated at the start of this review. Each identified gene will need to be examined to determine if its directional change with inactivity has been associated with risk factors or pathology of disease. Next, those genes whose altered expression by inactivity is associated with a disorder will require experiments for causality, i.e., the gene must be overexpressed or silenced to those levels found in healthy animals to determine whether it diminishes the risk factor or pathology and restores normal function. Notably, overexpression beyond those found in healthy animals can produce false positives. For example, overexpression of PGC-1α in mouse skeletal muscle increased type I fibers (64); however, voluntary wheel running does not cause a change in type I fibers in mice (104). Furthermore, the findings in voluntary wheel running are confirmed in most other training studies (see Ref. 41 for references). It is important to note the discrepancy between supramaximal overexpression using transgenic models and responses found in physiological models, as it is vital for an appropriate interpretation. In this example, one should not interpret the data to mean that PGC-1α could be involved in exercise-induced transitions to type I fibers since there is no evidence to support that there is a transition to type I fibers in physiological models of exercise. An additional limitation of this particular route of study needs to be recognized: most chronic diseases are polygenic; changing a single gene may not produce a preclinical phenotype.

SUMMARY

Humans likely have the potential for the most advantageous environment-gene interaction in their history on Earth; we are quite fortunate to be alive in this era. In a period of less than a half-century, knowledge has advanced from Watson and Crick (97) to a complete sequence of the human genome (53, 92). However, humans’ engineering of physical inactivity into their lifestyle has had the adverse effect of increasing the incidence of inactivity-induced chronic disease. The solution to this critical societal problem lies in a more advanced understanding of the maladaptations due to physical inactivity-gene interactions. Understanding physical inactivity-gene interactions will further our knowledge of gene-environment interactions, provide the molecular evidence required to further promote the primary prevention of chronic diseases through physical activity, identify those molecules that will allow early disease detection, and provide society with the information needed to counter the current strategy of increasing physical inactivity in our lives. Therefore, a fundamental question of biology is, how and why does the body adapt to physical inactivity?

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