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HIGHLIGHTED TOPIC | *Physiology and Pathophysiology of Physical Inactivity*

Metabolic disruptions induced by reduced ambulatory activity in free-living humans

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Thyfault JP, Krogh-Madsen R. Metabolic disruptions induced by reduced ambulatory activity in free-living humans. *J Appl Physiol* 111: 1218–1224, 2011. First published June 2, 2011; doi:10.1152/japplphysiol.00478.2011.—Physical inactivity likely plays a role in the development of insulin resistance and obesity; however, direct evidence is minimal and mechanisms of action remain unknown. Studying metabolic outcomes that occur after transitioning from higher to lower levels of physical activity is the best tool to answer these questions. Previous studies have successfully used more extreme models of inactivity, including bed rest, or the cessation of exercise in highly trained endurance athletes, to provide novel findings. However, these models do not accurately reflect the type of inactivity experienced by a large majority of the population. Recent studies have used a more applicable model in which active (~10,000 steps/day), healthy young controls are asked to transition to an inactive lifestyle (~1,500 steps/day) for a 14-day period. The transition to inactivity resulted in reduced insulin sensitivity and increased central adiposity. This review will discuss the outcomes of these studies, their implications for the cause/effect relationship between central adiposity and insulin resistance, and provide rationale for why inactivity induces these factors. In addition, the experimental challenges of directly linking acute responses to inactivity to chronic disease will also be discussed.

inactivity; skeletal muscle; insulin sensitivity; obesity

TYPE 2 DIABETES AND CENTRAL OBESITY

OBESITY and obesity-associated metabolic diseases are increasing at epidemic rates. The World Health Organization's (WHO) latest estimates indicate that ~400 million adults were obese (body mass index > 30 kg/m^2) globally in 2006 and predict that these numbers will rise to 700 million by the year 2015. This increase in obesity parallels a dramatic increase in the number of persons diagnosed with Type 2 diabetes (T2D). In 2009, WHO estimated that more than 200 million people worldwide have T2D, and it is estimated that worldwide T2D rates will double between the year 2000 and 2030 (46). Although excess adiposity in all regions can cause metabolic consequences, excess central adiposity (visceral adiposity) is most tightly linked to the development of T2D (1, 3, 9, 12, 13). The current dogma implies that central adiposity first develops, leading to inflammation and/or an increased storage of ectopic lipids in skeletal muscle and liver, which induces insulin resistance and ultimately leads to T2D (31), but this order of events has never been proven (33). The causes of both increased central obesity and type 2 diabetes are undoubtedly multifactorial and complex; however, we (5, 43) and others (15, 23) believe that a lack of regular exercise, or physical inactivity, plays a fundamental role. This hypothesis is backed by epidemiological evidence suggesting that physical inactivity plays a causal role in the development of T2D (20, 21) and obesity (10) while regular physical activity significantly lowers risk (2, 23, 24) for both conditions. While these studies strongly associate inactivity to T2D and obesity, historically, there have been a limited number of studies which experimentally impose physical inactivity for a defined period of time to confirm these causal links and examine mechanisms.

EXPERIMENTAL METHODS TO STUDY INACTIVITY IN HUMANS

It appears that the scientific community is beginning to appreciate the fundamental role that physical inactivity plays in the development of metabolic dysfunction, as a variety of studies with different inactivity models have been published in the last few years. A model for studying the direct mechanisms induced by physical inactivity is to transition human subjects

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or animal models from a higher to a lower level of physical activity for a defined period of time. Several different human inactivity models fit under this umbrella, including ceasing daily endurance exercise in endurance athletes, inducing bed rest, increasing sitting time, and lowering daily ambulatory activity. All of these models of inactivity induce detrimental physiological changes and provide important information for better understanding how inactivity can lead to metabolic dysfunction. It is our opinion that lowering daily ambulatory activity is the most applicable model for studying the role that inactivity has on the development of metabolic disease in everyday common living. Increasing daily sitting times, which lower ambulatory activity, would likely achieve the same goal. We view that other models like cessation of endurance exercise in competitive athletes or bed rest are scientifically interesting, and can induce important findings, but do not accurately recapitulate how inactivity is manifested in the daily lives of a large majority of individuals. For example, most individuals are not endurance athletes and do not transition down from extremely high levels of daily physical activity. Nor do most people transition to complete permanent bed rest as some low level of ambulatory activity is needed for daily life even in the most sedentary individual. There is a wide range in the number of steps (measure of ambulatory activity) reportedly taken by individuals in their daily life. Previous reports estimate that most free-living, nonexercising US adults take between 12,000 and 2,000 steps per day (6). Epidemiological evidence suggests that individuals at the higher range of activity better protect themselves from chronic disease risk, while those at the lower end increase their risk (23). Therefore, the most applicable human model for mimicking how a sedentary lifestyle increases risk for disease is to have individuals who obtain daily ambulatory activity on the upper end transition to the lower end of the spectrum for a defined period of time. However, the results of these studies are limited because they are the acute events that occur and are not directly linked to development of chronic disease. These experimental limitations are discussed in a latter section.

This review will examine the role that inactivity induced by transitioning from high to low daily ambulatory activity has upon insulin sensitivity/resistance and central adiposity, critical players in the development of metabolic and cardiovascular diseases. Earlier rodent "wheel lock" studies, which laid the foundation for the human studies, and have provided surprisingly similar results, will be discussed prior to review of studies in humans. The outcomes of these studies in relation to metabolic disease and their implications for the cause/effect relationship between central adiposity and insulin resistance will also be discussed. Finally, we will discuss the experimental challenges of linking acute responses to inactivity to overt chronic metabolic disease, which is ultimately needed to convince the scientific/medical community that inactivity is pathological and is a primary driver of metabolic dysfunction.

WHEEL LOCK STUDIES IN RODENTS

Booth and colleagues (27–30, 38) published a series of "wheel lock" studies to determine the mechanisms by which acute inactivity leads to metabolic dysfunction. Rats provided with voluntarily running wheels (VWR) in their cages will voluntarily run during the dark cycle. The running is not continuous but is intermittent in nature, and varies greatly dependent upon the strain and age of the rat. Running volumes can vary from ~1 up to 20 km over a 12-h dark cycle period but are typically consistent within experiments. In addition, the mitochondrial adaptations in skeletal muscle after VWR (29, 39) are usually very modest and pale in comparison to what is measured in rats forced to run on treadmills (11). Therefore, it could be argued that VWR in rats is analogous to higher daily ambulatory activity in humans, while treadmill running in rats would mimic programmed endurance exercise in humans. The addition of running wheels also allows rodents to be studied in active state, which is a much more accurate reflection of their phenotype than studies performed in sedentary rodents. The wheel lock model employed by the Booth group allowed rats to voluntarily obtain physical activity on VWR for a period of time (3–6 wk) followed by wheels being locked, which transitions rats to sudden inactivity (cage only movement). In these studies the rats would typically be transitioned from 5–10 km/day of running to cage-only activity. Rats whose wheels were locked for only 5 h (WL5) served as active controls, while those rats whose wheels were locked for longer periods of time, including but not limited to 29 h (WL29; 1 day), 53 h (WL53; 2 days), and 173 h (WL173; 7 days), were examined to determine how transitioning to inactivity and not receiving a daily dose of activity alters metabolic function. Rats who never had access to VWR served as a sedentary group (SED).

The wheel lock studies by Booth's group produced several novel outcomes, including important findings related to adiposity and insulin sensitivity (27, 28, 30). As expected, daily wheel running significantly increased insulin-stimulated glucose transport into isolated skeletal muscle (epitrochlearis), but locking the wheels and ceasing running for only 53 h (2 days) completely eliminated this effect (27) as insulin-stimulated glucose transport (when using submaximal insulin doses) dropped to levels measured in muscle from SED rats. The reduction in insulin-stimulated glucose transport was paired with reduced activation of the insulin-signaling pathway [reduced insulin receptor (IR) and Akt phosphorylation], and reduced GLUT4 protein content in epitrochlearis muscle after only 53 h of wheel lock. This evidence is intriguing because it indicates that there was a programmatic reduction at multiple levels of regulation, including insulin receptor, post-receptor signaling transduction, and regulation of GLUT4 content, which all culminates in reduced insulin-stimulated glucose transport into muscle. In addition, there was evidence that there were higher quantities of both protein tyrosine phosphatase 1B (PTP1B) and protein kinase c-Θ (PKCΘ) associated with the insulin receptor 2 days following wheel lock. Increased activation or content of both PTP1B (44) and PKC isoforms are strongly implicated in the development of skeletal muscle insulin resistance (22), but in this case, they seem to be playing a role in modulating insulin signaling in response to a transition to inactivity. Why these negative regulators of insulin signaling would be activated by a transition to inactivity and the degree to which molecules controlling insulin signaling are playing a pathological vs. nonpathological role are extremely interesting. As eloquently stated in an insulin-signaling review (47), the initiation of insulin signaling, itself, sets in motion negative feedback on insulin signaling at several levels. Following insulin stimulation, some mechanisms immediately act to terminate insulin's

effects through activation of lipid or protein phosphatases and through the induction of Ser/Thr kinases that phosphorylate and uncouple various elements along the insulin-signaling pathways. Other negative-feedback control mechanisms operate on a longer time scale, and involve a reduction in the cellular content of the IR, its substrates, and other signaling elements. Thus the activation of PTP1B or serine kinases like PKC, which reduce activation of the insulin-signaling cascade, are not pathological in origin, but are present to acutely or chronically "feed back" and regulate insulin action so that euglycemia is tightly maintained. Rather, it is another stimulus that converts these molecules toward a pathological process. As discussed later, inactivity may be an initiating stimulus or at least a permissive action for the conversion to a pathological condition of insulin resistance. Most importantly, the sudden loss of insulin action following cessation of daily running by wheel lock in rats was remarkably similar to a previous study in humans in which the cessation of daily endurance exercise lowered insulin sensitivity (hyperinsulinemic-euglycemic clamp) to the levels measured in sedentary individuals in just 60 h (2.5 days) (7).

Adipose mass also changed rapidly after wheel lock and the cessation of daily running (28, 30). Wheel lock for only 53 h (2 days) led to a 30% increase in epididymal fat mass and a 48% increase in omental fat mass (28). Additionally, increased mean cell volume and increased amount of lipid per cell was measured in the epididymal fat mass. This was also paired with a three- to fivefold increase in palmitate incorporation into triacylglycerol in the epididymal fat pads of WL53 compared with WL5 rats. Rats that undergo daily running on VWR have higher food consumption than SED rats for the first 3–4 days following wheel lock, putting the rats in a positive energy balance (30). Thus it could be assumed that positive energy balance due to increased food consumption and not the sudden transition to inactivity per se was the primary driver of an acute increase in adiposity. A follow up study examined this question. Laye et al. (30) tested if lowering food intake (pair-fed the same amount of food as consumed by sedentary rats who never ran) immediately after wheel lock, and thus putting the rats in a predicted neutral energy balance, would block the rapid increase in fat pad mass following the cessation of daily running (30). The pair-fed group was compared with another group of animals allowed to eat ad libitum following wheel lock. In this study, rats were provided VWR for 42 days and then the wheels were locked for 2 days (53 h) and 7 days (173 h). As before, rats whose wheels were only locked for 5 h served as active controls. Both ad libitum-fed rats and rats pair-fed to restore energy balance immediately following wheel lock experienced a similar, significant increase in fat pad mass. Retriperotoneal fat pad mass increased by ~100% and epididymal fat pad mass increased by ~40% following 7 days of wheel lock in pair-fed and ad libitum-fed groups. This evidence clearly indicated that transitioning from a state of high activity to inactivity increases fat pad mass, and that this effect was not simply due to maintenance of increased food consumption after transitioning to inactivity. Rather the inactivity itself altered both energy usage (insulin sensitivity) and storage (adipose mass), and perhaps these two factors are linked.

REDUCED AMBULATORY ACTIVITY IN HUMAN SUBJECTS

Pedersen and colleagues were intrigued by the wheel lock findings in rodents (personal communications from Booth and Pedersen) and set out to see if transitioning to inactivity for a short period of time would also lead to reduced insulin sensitivity and increased adiposity in humans (26, 37). Young, healthy men who were underwent high levels of daily physical activity (>10,000 steps/day) but that did not perform regularly programmed exercise were recruited to participate. Subjects were then asked to drastically reduce their daily physical activity for a period of 14 days. To achieve this objective, subjects were asked to avoid vigorous activities and choose sedentary lifestyle choices including taking a car instead of walking and taking the elevator instead of the stairs, etc. They were also asked to self-monitor their daily step count below a threshold of 1,500/ day. As a result, subjects with ~10,000 steps per day during their normal daily activities prior to the study reduced their daily steps to 1,500 steps/day, an 85% decrease during the 14 days of inactivity. Several measures including visceral adiposity, maximal oxygen uptake ($\dot{V}O_{2max}$), body composition, oral glucose tolerance tests (OGTT), insulin sensitivity (hyperinsulinemic-euglycemic clamp), and insulin signaling in skeletal muscle biopsies were performed at baseline and following 2 wk of reduced ambulatory activity.

Several unique body composition changes occurred following reduced ambulatory activity in healthy young men. Central adiposity (visceral adipose measured by MRS) increased significantly by 7% after the 14 days of reduced daily ambulatory activity (37). Interestingly, this was associated with a significant reduction in total body weight (loss of 1.2 kg) suggesting that the increase in central adiposity was not due to a gross increase in positive energy balance during the 14-day period of inactivity. These data uniquely matched the dramatic increase in fat pad mass measured in rats in the days following wheel lock, even when food intake was limited (30). Insulin sensitivity was also significantly altered after inactivity. Both the insulin response to a glucose tolerance test and an oral fat tolerance test were increased while the glucose infusion rate during a hyperinsulinemic-euglycemic clamp (insulin infused at 40 $mU \cdot m^{-1} \cdot m^{-2}$) decreased significantly. Hepatic glucose output (endogenous glucose production measured by [6,6-$^2H_2$]glucose infusion) during the clamp was not different after 14 days of reduced ambulatory activity, indicating that inactive skeletal muscle was the likely cause of reduced insulin action. Skeletal muscle biopsies taken before and during the clamp were analyzed to determine if insulin stimulation of insulin-signaling proteins were altered. It was revealed that 14 days of reduced activity significantly lowered insulin stimulation of Akt serine^{473} phosphorylation, proving that insulin signaling was indeed attenuated after inactivity.

Additional intriguing results showed that $\dot{V}O_{2max}$ significantly decreased by 7% and that lean body mass in the legs decreased significantly by 2.8%. Although not the focus of this review, both low fitness (25, 34, 41) and reduced muscle strength (32) are predictors of early mortality. Thus, not only did reducing activity increase central adiposity and lower insulin sensitivity, but it also altered two other measures tightly linked to increased risk for early death. Most importantly, these outcomes occurred in healthy young men who simply avoided

physical activity in their daily life for a period of only 2 wk while maintaining their normal dietary habits.

CENTRAL ADIPOSITY AND INSULIN RESISTANCE: THE ROLE OF INACTIVITY

As previously stated, central adiposity has been postulated to be a primary cause of insulin resistance (31). Both inactivity studies in rats and humans observed significant increases in central adiposity (visceral fat in humans and retroperitoneal in rodents) at the same time that there was a significant reduction in insulin sensitivity of skeletal muscle. This suggests that the changes occur independently or that reduced insulin sensitivity contributes to a repartitioning of energy substrates into storage after a transition to inactivity. Bed rest studies, a more extreme model of inactivity, show changes in glucose and fat metabolism that support a repartitioning of energy (4), including a recent report focused on changes in adipose tissue (18). Newer studies in the rodent wheel lock model also show evidence for the repartitioning of energy as there are rapid changes in lipid oxidation and pathways controlling lipid synthesis in muscle, liver, and adipose in the days following a transition to inactivity (29, 38). The exact mechanisms are unknown but could be tied back to control of insulin sensitivity at the level of the muscle. Reduced insulin sensitivity leads to larger insulin responses and in some cases larger glucose responses after every meal. Insulin promotes lipid synthesis, and therefore, elevated insulin responses following each meal could promote greater fat deposition in adipose. Moreover, if glucose levels are elevated after each meal, it would provide more opportunity for adipose to take up glucose for de novo lipogenesis and subsequent storage. Data recently accepted for publication from our lab (32a) using continuous glucose monitors shows that acute drops in ambulatory activity for only 3 days do significantly increase the magnitude of blood glucose excursions after meals. In addition, some evidence supports diminishing insulin sensitivity to be linked to developing adiposity in longitudinal studies. The rate of change in visceral fat was positively associated with annual increases in fasting insulin in children over a 5-yr period (11) while fasting insulin was associated with an increase in waist-hip ratio over 4.4 yr in adult women (14). However, it is hard to discern cause and effect from such studies, leaving this a contentious topic. A recent study did show that a 5% weight regain and a subsequent significant increase in visceral fat mass was not tied to insulin resistance (measured by fasting insulin and glucose) if subjects exercised regularly to maintain insulin sensitivity during the weight regain, suggesting that two factors are not necessarily connected in any fashion (42).

RESPONSE TO INACTIVITY: PRESERVATION OR PATHOLOGY

An important question is "why does an acute transition to inactivity lead to reduced insulin sensitivity and increased adiposity?" The answers most likely relate to the survivability of species over millions of years. A sudden transition to inactivity stimulates a need to match lower glucose transport with reduced ATP demands in muscle. This was an adaptation critical for survival as it preserves the limited amount of glucose in circulation and also provides excess energy for storage in adipose, energy that can be liberated later when activity ensues or after short-term fasting. As reviewed previously by Chakravarthy and Booth and colleagues (5, 8), glucose preservation (reduced insulin sensitivity in muscle) and a quick increase in adiposity following inactivity would be critical for surviving periods when food shortage was low. This fits in the "thrifty" hypothesis put forward by Neel (36), which hypothesized that there was evolutionary selection for individuals that were "exceptionally efficient in the intake and/or utilization of food," the rationale being that a greater capacity for storage during times of plenty would provide a survival advantage due to greater fuel reserves during times when food was scarce. Figure 1 previously described by Chakravarthy and Booth (8) depicts the cycles, driven by food availability and activity, that our metabolic pathways were designed to follow. After procuring food there were periods of relative inactivity that allowed for energy substrates to be replenished in skeletal muscle [glycogen and triglycerides (TG)] and storage of excess glucose and TG in adipose. These energy stores were then depleted during the next bout of activity to procure food through the activation of contraction-induced metabolic enzymes/pathways [Glut4, AMP-activated protein kinase (AMPK), lipoprotein-lipase (LPL)]. Food shortage with or without activity would have also depleted energy stores. These cyclic periods are in extreme contrast to our current environment in industrialized

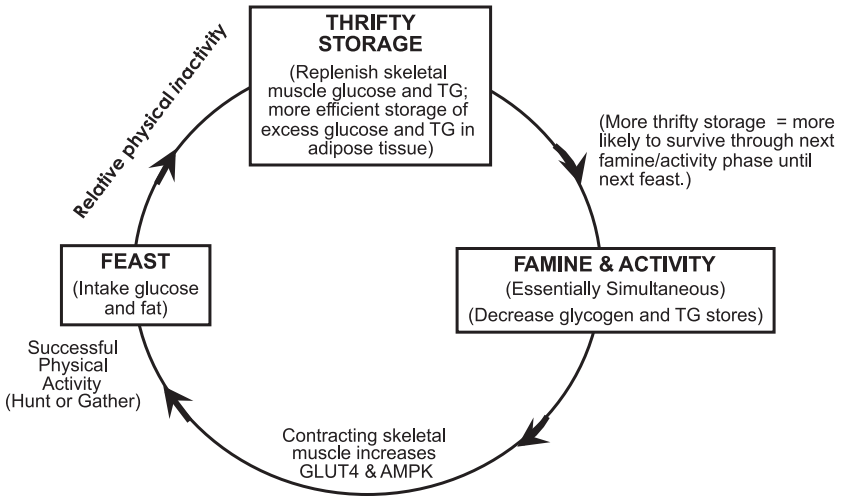

Fig. 1. Food and physical activity cycle. As presented previously by Chakravarthy and Booth (8), in ancient times there were cyclic patterns of food consumption and physical activity. Food was located through high levels of physical activity (hunting and gathering). During and following food consumption there were short periods of relative inactivity that would allow for the "thrifty" storage of energy in muscle and adipose. This stored fuel would then provide energy for activity needed to find more food and/or to survive a period of food shortage until the next source of food was procured. The thrifty mechanism of efficiently storing energy was likely an evolutionary adaptation that is conserved today. TG, triglycerides; AMPK, AMP-activated protein kinase; LPL, lipoprotein lipase. [Reproduced from Chakravarthy and Booth (8).]

nations in which adequate physical activity has been engineered out of our daily lives and we constantly have available energy-rich foods. Figure 2 (8) depicts how the cessation of these cycles impacts insulin sensitivity and adiposity, a hypothesized chain of events that strikingly fits the human studies discussed in this review. As a result of chronic inactivity and constant nutrient excess, insulin sensitivity would continue to deteriorate over time; moreover, we posit that the low energy demand and reduced insulin sensitivity is obligatory in providing a permissive state in which the initiation of pathological processes (inflammation, oxidative stress, and lipid intermediates) believed to activate insulin resistance can occur (34, 45). This is not dismissing a key role for these factors to disrupt insulin sensitivity, but rather suggesting that constant inactivity is the primary causal event. The second outcome of the breaking of this cycle is the continuing expansion of adipose tissue. A continuous expansion of adiposity leads to the ectopic storage of lipids in muscle and liver (34) and the activation of inflammation (45), both of which are linked to the development of insulin resistance. Moreover, the expansion of central adiposity paired with insulin resistance form the basis for the metabolic syndrome.

It is largely agreed upon by researchers with combined metabolic and exercise research backgrounds that inactivity is a primary driver for the development of insulin resistance (15, 40). Recent reviews have elegantly presented a wide range of epidemiological evidence that physical inactivity is a primary driver for the development of insulin resistance and T2D, while physical activity provides protection (23, 40). Interesting observations supporting the link between inactivity and insulin resistance and overall metabolic dysfunction can also be observed in animal models. In fact, we are not aware of studies in which insulin resistance can be induced in animals if they are permitted or forced to obtain a certain volume of physical activity. Both high-fat diets and hyperphagic-dietary overconsumption induce insulin resistance in sedentary rodent models; however, if the rodents in these studies are allowed to obtain physical activity (VWR, treadmill running, or swimming), insulin resistance does not develop. For example, we have shown that providing VWR to Otsuka Long Evans Tokushima Fatty rats (OLETF; hyperphagic-obese model prone to T2D) out to 40 wk of age prevents insulin resistance and the development of T2D unequivocally (39). This protection occurs even though the running OLETF have a large decrease in running distance by 40 wk of age (~4 km/day by 40 wk of age down from ~11–12 km/day at 12 wk of age). In addition, the running OLETF consume more food per body weight than do sedentary animals. Moreover, insulin resistance in muscle is dramatically improved if chronic exercise is provided as a treatment in animal models (17, 43). In addition, multiple studies have found that one bout of exercise can acutely restore insulin-stimulated glucose transport in muscle that was previously insulin resistant (43). Although the acute effects of exercise to improve insulin sensitivity do not always track with improvements in insulin signaling or a reduction of putative proteins and metabolites involved in insulin resistance, the endpoint is that insulin-stimulated glucose transport is dramatically improved (17, 43). Our interpretation of these data is that inactivity and a resultant low level of energy expenditure in skeletal muscle are obligatory for the development of insulin resistance.

Unfortunately, the larger scientific and medical community does not seem to appreciate the links between inactivity and insulin resistance. There are logical reasons for this disconnect. First, it is our opinion that most of the medical community believes that exercise or increased physical activity is something that can "improve" health rather than a physiological stimuli that is absolutely "necessary" for normal function and health. As already stated our genes and metabolic pathways were engineered to survive over millions of years in which we had to be extremely active to procure food. Thus it is logical that placing those same genes in a new environment of extremely low activity and energy expenditure could lead to metabolic ramifications. A second reason for the underappreciated connection between inactivity and insulin resistance is the difficulty in producing direct, mechanistic evidence for how physical activity or inactivity modulates insulin-stimulated glucose transport. For example, Holloszy (19) commented,

> . . . essentially no progress has been made in elucidating the mechanism(s) responsible for mediating this (postexercise increase in insulin sensitivity) phenomenon. This lack of progress is not too surprising when viewed in light of the very slow progress that has been made in explaining how insulin stimu-

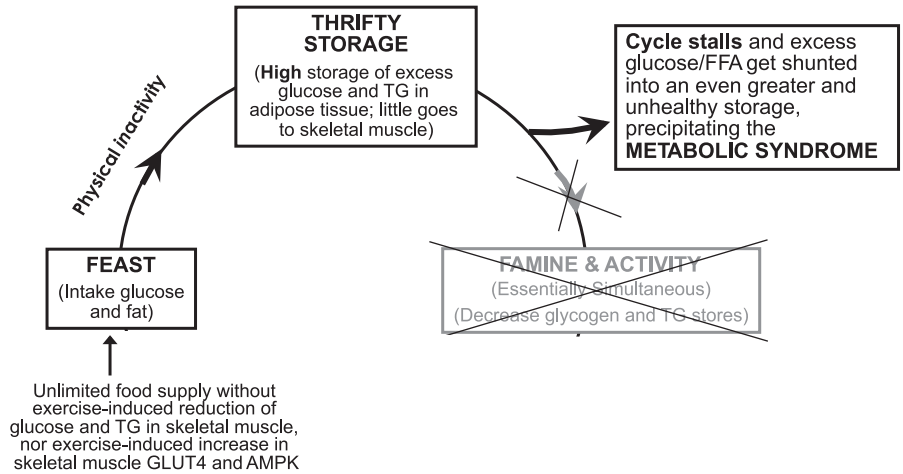

Fig. 2. Stalling of the food and physical activity cycle with inactivity. As presented previously by Chakravarthy and Booth (8), the ability for thrifty storage still exists, but physical activity and food shortage have been removed. Because there is chronic physical inactivity paired with continuous food consumption, energy stores do not become depleted. This leads to reduced glucose transport (reduced insulin sensitivity) into skeletal muscle and gradually expanding adiposity. The continuance of physical inactivity and excessive energy storage provides a permissive environment in which pathological mechanisms leading to chronic diseases like the metabolic syndrome can develop. FFA, free fatty acids. [Reproduced from Chakravarthy and Booth (8).]

lates glucose transport despite enormous expenditure of effort and resources by hundreds of talented investigators over the past 60 years. . . . Clearly, these are extremely complex processes. . . . I think that the additional research needed to explain how glucose transport and insulin sensitivity are regulated will keep all of us who are working in this area, including those just beginning their careers, intellectually stimulated and motivated for the rest of our research careers.

Studies like the ones discussed in this review show that transitioning from high to low levels of physical activity for a long period of time dramatically lowers insulin sensitivity and increases adiposity. We do not have clear-cut evidence that these short-term changes play a causal role for pathological alterations and overt chronic disease. For example, the reduction in insulin sensitivity with inactivity is by no means a pathological condition; rather it is simply an adjustment to a different energy demand in muscle. As shown by previous studies, the restoration of activity levels will quickly restore insulin sensitivity (16) and although we can hypothesize that it is only when inactivity ensues for long periods of time that a "permissive" state for the pathology of insulin resistance can occur, it is difficult to prove this link even if long-term studies can be applied. Although we are certain that inactivity is an underlying fundamental cause of insulin resistance and of a decline toward frank T2D, mechanistically making this link in short-term studies is impossible because it takes an extended period of time for a chronic disease to develop. Unfortunately, these problems do not mesh with the present methods of reductionism in using knockout or overexpression of single genes in rodents, even though we know chronic diseases are polygenic in nature. Additionally, these concepts do not apply well to the practice of studying insulin resistance and obesity in caged-sedentary rodents.

CONCLUSION

Transitioning from high to lower levels of ambulatory activity for only 14 days caused reduced skeletal muscle insulin sensitivity and increased central adiposity. Although it is difficult to link these acute changes to the development of chronic disease over many years, inactivity-induced changes are headed in a pathological direction. Therefore, we contend that chronic inactivity provides a permissive environment for the development of pathological processes. However, more work in similar models is needed to connect the acute to the chronic changes, determine mechanisms of action, and to convince the scientific and medical community of the primary role that inactivity has in the development of obesity and T2D.

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DISCLOSURES

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