HIGHLIGHTED TOPIC | Physiology and Pathophysiology of Physical Inactivity

Physical inactivity as the culprit of metabolic inflexibility: evidence from bed-rest studies

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Bergouignan A, Rudwill F, Simon C, Blanc S. Physical inactivity as the culprit of metabolic inflexibility: evidence from bed-rest studies. J Appl Physiol 111: 1201–1210, 2011. First published August 11, 2011; doi:10.1152/japplphysiol.00698.2011.—Although it is no longer debatable that sedentary behaviors are an actual cause of many metabolic diseases, the physiology of physical inactivity has been poorly investigated for this purpose. Along with microgravity, the physiological adaptations to spaceflights require metabolic adaptations to physical inactivity, and that is exceedingly well-simulated during the ground-based microgravity bed-rest analogs. Bed rest thus represents a unique model to investigate the mechanisms by which physical inactivity leads to the development of current societal chronic diseases. For decades, however, clinicians and physiologists working in space research have worked separately without taking full awareness of potential strong mutual questioning. This review summarizes the data collected over the last 60 years on metabolic adaptations to bed rest in healthy subjects. Our aim is to provide evidence that supports the hypothesis that physical inactivity per se is one of the primary causes in the development of metabolic inflexibility. This evidence will focus on four main tenants of metabolic inflexibility: 1) insulin resistance, 2) impaired lipid trafficking and hyperlipidemia, 3) a shift in substrate use toward glucose, and 4) a shift in muscle fiber type and ectopic fat storage. Altogether, this hypothesis places sedentary behaviors upstream on the list of factors involved in metabolic inflexibility, which is considered to be a primary impairment in several metabolic disorders such as obesity, insulin resistance, and type 2 diabetes mellitus.

fat oxidation; insulin resistance; ectopic fat storage; sedentary behaviors; lipolysis

Our societies have constructed during the 20th century an ecological niche in which sedentary behaviors and junk food became the new reference of living. Although this evolution is considered as an improvement in our living conditions, it created a mismatch between our evolutionary history and the environment for which humans adapted. Nowadays, exercise is typically presented as a therapy to several chronic diseases (16). This transition has even altered our appreciation of physical activities itself. Although 65% of the National Health and Nutrition Examination Survey American population self-reported to be as active as recommended by national guidelines, objectively measured, physical activity by accelerometry showed this number to be only 5% (70). This is a rather important observation when considering that physical inactivity has been classified as the second cause of death in the United States (47) based on the 35% self-reported inactive people.

The hazards of physical inactivity have been described for a long time (43). A growing body of data suggests that reduced physical activity is causative in the development of modern chronic metabolic diseases, including obesity, insulin resistance, dyslipidemia, type 2 diabetes mellitus (T2D), hypertension, and others (16). Some data suggest that sedentary behavior is an independent predictor of metabolic risk, even when exercise is performed at a level that meets current recommendations (54). The causal relationships between physical inactivity and metabolic diseases are essentially based on epidemiological studies or on the indirect beneficial effects of exercise training. None of these studies provide, however, evidence to support a cause-and-effect relationship. Our poor knowledge on physical inactivity physiology can in part be attributed to the paucity of models to induce long-term physical inactivity in healthy subjects that account for the confounding effects of the positive energy balance induced by physical inactivity itself.

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Along with microgravity, the physiological adaptations to spaceflights require metabolic adaptations to physical inactivity that is exceedingly well simulated during the ground-based microgravity bed-rest analogs. In addition to space medicine-related questions, bed rest thus represents a unique model to investigate the mechanisms by which physical inactivity leads to the development of current societal chronic diseases. The degree of physical inactivity encountered during bed rest may be seen as too extreme compared with that seen in the general population, who spend more time sitting and with some level of movement rather than strictly lying down. However, it is important to note that the physical activity level (PAL) measured during bed-rest studies is close to that measured in sedentary individuals, i.e., a PAL of ~1.4–1.5 (5, 14), because of fidgeting movements in the bed. Bed rest remains a unique model to investigate the basic mechanisms of adaptation to short- or long-term physical inactivity in healthy subjects. For decades, clinicians and physiologists working in space research have worked separately without full awareness of potential strong mutual questioning.

The concept of metabolic inflexibility was first proposed ten years ago by Kelley et al. (33) from several metabolic disorders such as obesity, insulin-resistance, and T2D. These diseases are characterized by a metabolic deregulation that impairs the capacity to increase fat oxidation when fatty acid availability is increased and to switch from fat to glucose as the primary fuel source after a meal (19). Because these adaptations were not normalized after weight loss in some studies (11), several authors suggested that they might represent a primary impairment responsible for the development of the diseases. In this review, we provide evidence collected over the last 60 years from healthy, bed-rested subjects to support the hypothesis that physical inactivity per se is one of the primary causes involved in the development of metabolic inflexibility, even when changes in energy balance are not detectable. The data that support our hypothesis are divided into four main parts. The first section is dedicated to insulin resistance, the second, to the alterations in lipid trafficking, and the third, to the changes in the fuel mix being oxidized during bed rest. The fourth part provides evidence that insulin resistance and the decreased capacity to use fat as fuel during physical inactivity may trigger a generalized ectopic fat storage. We will provide some recent evidence to highlight the role of physical activity level in the regulation of metabolic flexibility. Last, we will combine all these data and describe the link between physical inactivity and metabolic inflexibility.

**PHYSICAL INACTIVITY INDUCES INSULIN RESISTANCE**

**Whole body evidence from bed-rest experiments in humans.** Numerous bed-rest studies of different durations showed a decrease in insulin sensitivity (1, 7, 8, 12, 22, 25, 38–40, 45, 46, 51, 57–59, 66, 67, 74). To our knowledge, Lutwack and Whedon (40) were the first in 1959 to have reported abnormal intravenous glucose tolerance tests after 1–3 wk of bed rest in healthy subjects. Other early reports in the 1970s also observed glucose intolerance and hyperinsulinemia following an oral glucose tolerance test (OGTT) after 10–14 days of bed rest (22, 38, 39, 51). Although the acute response of insulin to bed rest (1–2 days) has not been investigated, Yanagibori et al. (74) observed during a 20-day bed-rest period that an increase in insulin and glucose responses during an OGTT appears as early as day 3 in 13 females and 10 males. In this same study, bed-rest studies also confirmed the development of insulin resistance in both sexes (7, 8, 12).

Studies were conducted to understand the mechanisms involved in the reduced whole body insulin sensitivity by specifically investigating the response to insulin in the main insulin-sensitive organs, i.e., skeletal muscle, adipose tissue, and liver. In a 7-day bed rest in six healthy men, Mikines et al. (45, 46) observed a decreased insulin action at muscle level on glucose uptake and glycogen storage. Even if the subjects were allowed to get up every other day to shower, Tabata et al. (68) also showed a 16% decrease in vastus lateralis glucose transporter 4 (GLUT-4) concentrations in nine healthy males after 20 days of bed rest. Altogether these results indicate the development of insulin resistance at the muscle level. No modification on hepatic glucose production was observed at both physiological and supraphysiological insulin concentrations in the males (45, 46, 67). However, by using stable isotopes to track endogenous and exogenous glucose metabolism, we observed that insulin resistance was only developed at the muscle level in men after 7 days of bed rest, as in the previous studies, but at both muscle and liver levels in women (12). This suggests a sex effect on liver insulin sensitivity during bed rest.

With regard to the adipose tissue insulin sensitivity, although the β-adrenergic receptors showed an increased sensitivity (4) during bed rest, plasma catecholamines are reduced (14), indicating a decreased activity of the sympathetic nervous system that does not allow an increase in lipolysis. On the basis of the fasting decrease in plasma free fatty acids (FFA) observed and increased fasting insulin in men and women after 7 days of bed rest, we can assume that physical inactivity does not reduce adipose tissue insulin sensitivity in both sexes (12). In support of that, recent bed-rest studies even associated whole body insulin resistance with a whole body reduction in lipolysis in male subjects (1, 2). Except in a very recent study (27) described later in this review, adipose tissue in the context of physical inactivity has been poorly investigated, and further studies are clearly needed.

Most of the above studies have a major limitation: they did not tightly control the diet of the subjects. An adequate nutrient supply to accurately derive the true effects of bed rest alone is of particular importance. A positive energy balance due to overfeeding will be a confounding factor that exaggerates the deleterious effects of physical inactivity (10). Thus the 67% increase in insulin response recently observed (25) may be due to the fact that subjects were provided with their habitual diet. Mikines et al. (45, 46) reduced energy intake by 15% only during the last 3 days of the bed rest. Furthermore, in the early study of Dolkas and Greenleaf (22), volunteers received a very high energy intake (3,073 kcal/day). Increased plasma leptin levels at the end of our first 7-day bed rest studies (13), with leptin being a biomarker of energy intake (18, 56), indicate that our subjects were overfed. The diet macronutrient composition also influences the bed-rest outcomes. In a crossover design, 60-h bed rest in eight males (2 days of washout) with either a high-carbohydrate diet (70% of energy intake) or a high-saturated-fat diet (45% of energy intake as fat and 60% of saturated fatty acid), Settler et al. (65) showed that insulin
sensitivity decreased by 24% with the high-saturated-fat diet but did not change with the high-carbohydrate diet. Because the lack of control on energy balance in early studies questioned the impact of physical inactivity per se on insulin sensitivity, we recently performed bed-rest studies, one study of 2 mo in women (8) and one of 3 mo in men (7) during which we tightly controlled the diet to clamp fat mass. Contrary to others (1, 2), we clamped fat mass rather than body mass, because due to bed-rest-induced muscle atrophy, a weight-clamping approach tends to increase fat mass (76), which reflects a positive energy balance. Tests investigating energy status of the volunteers confirmed that we succeeded (5). Interestingly, we showed that physical inactivity per se yet induces an increase in plasma insulin concentration without changes in plasma glucose concentration in fasting conditions and after a standard meal (Fig. 1). These results indicate that even in physiological conditions (i.e., not in supraphysiological insulinemic clamp) physical inactivity leads to the development of insulin resistance in both postabsorptive and postprandial situations (7, 8). A recent study (64) investigated the effect of 1 day of sitting, a level of physical inactivity closer to that observed in the general population than strict bed rest, on insulin action. The authors showed that with and without energy surplus, reduced physical activity considerably alters insulin action. The fact that this effect still occurred when food intake matched energy expenditure emphasized the deleterious effects of physical inactivity alone.

All of these studies only studied lean healthy subjects without any genetic predisposition to obesity or T2D. Considering the increasing prevalence to these chronic diseases and the fact that the general population tends to become more and more sedentary (26), it appears relevant to investigate the interaction between physical inactivity and the predisposition to obesity and T2D. In this line, some authors investigated the effects of 9–10 days of bed rest in healthy lean males (control group); in males with a first-degree relationship of diabetes (FDR); and in males with a low birth weight (LBW), known to be at risk to develop T2D in adulthood (1, 2, 60). By investigating whole body and forearm insulin sensitivity using a hypsinsulinemic euglycemic clamp, Sonne et al. (60) reported that bed rest induces a marked reduction in whole body

![Fig. 1](image_url)

**Fig. 1.** Whole body and muscle metabolic alterations induced by 2 mo of bed rest in women postprandially following the ingestion of standard breakfast and lunch. TG, triglyceride; FA, fatty acid; NEFA, nonesterified FA; CHO, carbohydrate; AUC, area under the curve; *P < 0.05 vs. active state. [Panel at bottom left reproduced from Trappe et al. (68a).] [All the other panels modified from Bergouignan et al. (8). Copyright 2009 American Diabetes Association. Modified with permission from The American Diabetes Association.]
skeletal muscle and vascular insulin sensitivity in both control and LBW groups with more pronounced changes in the control group. Although insulin resistance was already present before to bed rest in the FDR group, these subjects still displayed a decrease in insulin sensitivity in response to bed rest. In these three groups, insulin resistance was fully accounted for by nonoxidative glucose metabolism, but hepatic insulin resistance only occurred in the groups with a predisposition for T2D (1, 2). It should however be noted that although not significant, the reduction in the hepatic glucose production was about the same magnitude in the control group (+35%) compared with the FDR group (+36%) (2).

In conclusion, these bed-rest studies provided indisputable evidence that physical inactivity per se induces a reduction in the whole body insulin sensitivity associated with the development of insulin resistance in muscle but not in adipose tissue. The liver remains an important area to investigate, especially given the recent data associating physical inactivity with characteristics of nonalcoholic fatty liver diseases.

Mechanistic evidence from bed-rest experiments in humans and analogs in animals. The classical insulin-signaling pathways can be summarized as follows. Skeletal muscle glucose transport is acutely regulated by insulin through the coordinated actions of several proteins. Briefly, insulin activation of tyrosine kinase in the β-subunit of the insulin receptor leads to tyrosine phosphorylation of insulin receptor substrate 1 (IRS-1). Phosphorylated IRS-1 then interacts with the p85 regulatory subunit of phosphatidylinositol-3-kinase (PI3K). Activated PI3K subsequently activates phosphoinositide-dependent kinases, which regulate the serine/threonine protein kinase (Akt, also known as protein kinase B). Although the specific role of Akt in muscle glucose remains controversial, it seems to conduct to the translocation of GLUT-4 to the plasma membrane to facilitate glucose transport via a diffusion process. In addition, the stress-activated p38 mitogen-activated protein kinase (p38-MAPK) may negatively interact with the upstream of the insulin-signaling cascade, particularly IRS-1, inducing insulin resistance (23).

Those pathways were investigated in animal models of physical inactivity. Using the hindlimb tail paradigm, O’Keffe et al. (49) showed that after 1 day of suspension, female rats have a decreased glucose tolerance and reduced stimulated glucose uptake. This acute development of insulin resistance was mainly attributable to changes in p38-MAPK phosphorylation, as it was noted by others (41), but not to changes in insulin receptor beta (IR-beta)/IRS1/PI3K/Akt signaling pathway. After 3 and 7 days of suspension, insulin resistance was however associated with decreased insulin signaling pathway through IRS1 and PI3K and with increased p38-MAPK (50), suggesting that PI3K-independent mechanisms may also play a role in the adaptations to suspension.

Another model has been developed to study the effects of physical inactivity in rats: the wheel lock model. After a certain period during which rats naturally run in their cage, the investigators lock their wheel. This model better simulates the decrease in habitual physical activity observed in the general population than the hindlimb unloading model that is closer to immobilization. By using this model (34–37), a rapid decrease in skeletal muscle insulin sensitivity has been associated with an expansion of intra-abdominal fat storage. The authors especially observed a lower insulin-stimulated 2-deoxyglucose uptake into the epitrochlearis after 53 h of cessation of daily running (34). This impaired muscle glucose transport was associated with a decrease in insulin binding, IR-beta, submaximal insulin stimulated IR-beta tyrosine phosphorylation, and GLUT-4 level. Akt/protein kinase B Ser473 phosphorylation was also reduced after 53 h, suggesting that both upstream and downstream insulin signaling was diminished following running cessation.

Alibegovic et al. (3) investigated the mechanisms involved in the development of insulin resistance by using the microarray technique in 20 healthy men. Bed rest altered the expression of >4,500 genes and downregulated 34 pathways, predominantly those of genes associated with mitochondrial function, including the peroxisome proliferator-activated receptor-γ coactivator-α (PGC1α) that regulates oxidative phosphorylation (OXPHOS) in the mitochondria. Expression of several candidate genes involved in T2D was also impaired, such as the expression of PGC1α and OXPHOS genes in general, suggesting a reduced oxidative capacity. Likely related to the depressed PGC1α expression, a reduced expression of vascular endothelial growth factor A (VEGFA), which regulates the degree of capillarization and microvascular flow and thereby insulin action, was also observed. Hexokinase 2 (HK2), the protein that phosphorylates glucose after its entrance in the cell, and ras-related associated with T2D (RRAD) are considered the most prominent down- and up-regulated transcriptional alterations in skeletal muscle from diabetic patients that contribute to the altered insulin response and muscle glucose transport (29). The reduction in HK2 gene expression and the increase in RRAD level suggest that physical inactivity triggers modifications similar to those observed in T2D. The fact that 4 wk of intensive retraining did not completely normalize the expression of several metabolic genes underscores the importance of avoiding even short periods of physical inactivity.

These authors further observed an increase in genes involved in inflammation and endoplasmic reticulum stress in response to insulin stimulation during bed rest. Other studies have reported an upregulation of proinflammatory markers (10, 44) whereas some others did not (25). This is also true for oxidative stress (10, 42). Inflammation and oxidative stress are however processes known to negatively impact insulin sensitivity and should receive a greater attention in future bed-rest studies investigating the mechanisms underlying the development of insulin resistance. This appears even more important when considering that oxidative stress has been involved in muscle atrophy during disuse and that there is a tangled relationship between muscle fiber type, oxidative stress, and insulin sensitivity.

PHYSICAL INACTIVITY AFFECTS LIPID TRAFFICKING BETWEEN ADIPOSE TISSUE AND MUSCLE

Evidence from bed-rest experiments in humans. The whole body insulin resistance induced by bed rest is concomitant with the development of hypertriglyceridemia in both sexes (7, 8, 25, 73) (Fig. 1). From a mechanistic point of view, these higher levels of plasma triglycerides can be due to an increased adipose tissue lipolysis, a decreased plasma fat clearance, or both.
As we previously noted, whole body lipolysis is reduced during bed rest in subjects with or without a predisposition to T2D (i.e., LBW subjects) (1). The decrease in the whole body lipolysis in the subcutaneous femoral adipose tissue seems to be related to a decrease in hormone-sensitive lipase (HSL) activity in both groups (1). Højberre et al. (27) compared glucose uptake and lipolysis from subcutaneous abdominal and femoral adipose tissue by microdialysis in healthy subjects and in offspring of patients with T2D. The aim was to investigate whether physical inactivity would unmask defects of adipose tissue metabolism in FDR subjects. Although 10 days of bed rest significantly decreased lipolysis and tended to increase glucose uptake in the subcutaneous femoral adipose tissue in both control and FDR subjects, subcutaneous adipose tissue glucose uptake only increased in control subjects. Thus physical inactivity is as deleterious in control as in FDR subjects and even tends to attenuate the differences in glucose uptake subcutaneous adipose tissue that was observed between the two groups before bed rest. In summary, these results suggest that bed-rest-induced hypertriglyceridemia is not due to a higher lipolysis but likely caused by an altered plasma fat clearance.

Few human studies investigated fat uptake by peripheral tissues in humans. We determined the plasma metabolic fate of dietary fat by using stable isotope labeling (8). We showed that 2 mo of bed rest in women increases the spillover of nonesterified fatty acid (NEFA) released after hydrolysis of lipoprotein-triglycerides (chylomicrons or VLDL) by lipoprotein lipase (LPL) (Fig. 1). This higher NEFA spillover suggests that NEFAs are less taken up by peripheral tissues. This result is in accordance with a diminished gene expression of skeletal muscle LPL and FAT/CD36 (Fig. 1). Muscle atrophy also likely contributes to the lower plasma fat clearance and indirectly to hyperlipemia. To our knowledge, no data on liver and adipose tissue fat uptake are available during bed rest. Such studies are required to determine the respective role of these three main peripheral tissues in the development of hyperlipemia, which is strongly related to the development of insulin resistance.

Evidence from analogs in animals. Studies in rats using the hindlimb tail paradigm (9) showed that from 11 h to 11 days of inactivity induces a diminution of 80% of the muscle LPL activity, supporting the fact that physical inactivity decreases muscle fat uptake. Using the wheel-locked model, Booth et al. (15) further investigated in a nicely conducted series of experiments the effects of physical inactivity on lipid metabolism at the adipose tissue level along with the alterations in insulin sensitivity previously described. After 53 h of wheel-running cessation following 21 days of running, the authors measured a 25–48% increase in epididymal and omental fat pad weights, respectively (35). This increase in fat storage was associated with increased palmitate incorporation into triacylglycerol in epididymal fat in relation to an increase in protein level and activity of mitochondrial glyc erol-3-phosphate acyltransferase 1 (mtGPAT) (36), a key regulator of triacylglycerol synthesis. These changes were associated with increases in both plasma insulin and triglycerides (34). Interestingly, the enlargement in abdominal fat mass was observed in both ad libitum and pair feeding, suggesting that fat storage is the result of physical inactivity per se. The increase in epididymal, perirenal, and retroperitoneal fat masses was due to an increase in fat cell number, in the absence of changes in adipocyte size (37). In other words, these data indicate that physical inactivity promotes fat storage through adipocyte hyperplasia rather than hypertrophy.

Taken altogether, these results collected in both humans during bed-rest experiments and in rats using analogs suggest that physical inactivity shunts the delivery of plasma lipids away from muscle to adipose tissue but also stimulates, at least in rats, lipogenesis. This altered trafficking is likely concomitant (as a cause or a consequence) with an altered fat partitioning between oxidation and storage in muscle.

PHYSICAL INACTIVITY DECREASES FAT OXIDATION

Evidence from bed-rest experiments in humans. In normal conditions, the switch in fuel oxidation depends on the type and amount of nutrient (glucose, fatty acids, and amino acids) available for oxidation at the cellular level and is regulated through the activation or inhibition of specific metabolic pathways. In all bed-rest studies, a shift in fuel metabolism is observed in favor of carbohydrate oxidation and in detriment of lipid oxidation (Fig. 1). Importantly, this shift is independent of energy balance (63). The increase in nonprotein respiratory quotient (NPRQ) varies between 4 and 14% according to the duration of the bed rest (7, 8, 12). For example, 3 mo of bed rest induces in healthy lean men (7) a decrease of 37% in lipid oxidation and an increase of 21% in carbohydrate oxidation in postabsorptive situations. Similarly, changes of −40% and of +6% in lipid and carbohydrate oxidation are, respectively, observed in postprandial conditions.

The reduction in lipid oxidation is in fact more complex. It is well known that lipid oxidation depends on the length and the degree of saturation of the fatty acids: the shorter the carbon chain and higher the number of unsaturations, the greater is the oxidation (21). Using a double-labeling fatty acid method, we recently showed that physical inactivity differently alters the metabolic fate of dietary saturated and monounsaturated fatty acids (7, 8). Although bed rest does not affect dietary monounsaturated fatty acid (oleate) oxidation, it significantly decreases dietary saturated fatty acid (palmitate) oxidation in both healthy males and females (Fig. 1). This reduction in oxidation was likely in favor of incorporation of dietary saturated fatty acids into intramuscular lipids (Fig. 1) (8). Although we do not have a clear explanation for these striking observations, we submitted a hypothesis in a recent review (6). Briefly, carnityl palmitoyl transferase I (CPT-I) regulates the entrance of fatty acids into mitochondria and thus fat oxidation. mtGPAT regulates the first step of glycerolipid biosynthesis and thereby triglyceride synthesis. Because both mtGPAT and CPT1 are located on the outer mitochondrial membrane, they can compete for acyl-CoAs and thus reciprocally regulate the partitioning of fatty acids between degradative and biosynthetic fates in liver and muscle. The coordinated regulation of CPT1 and mtGPAT is mediated by AMP-activated kinase (AMPK). AMPK is an energy sensor that is influenced by physical activity; it is stimulated by exercise but reduced by physical inactivity. An increase in AMPK reduces malonyl-CoA concentration, which attenuates the inhibition of CPT1 and thereby increases fat oxidation. Conversely, it inactivates mtGPAT, which reduces triglyceride synthesis. A
Mechanistic evidence of the shift in fuel use from bed rest in humans and analogs in animals. It is important to note that changes in fuel use are independent of the bed-rest-induced muscle atrophy, i.e., changes in metabolically active mass. Nevertheless, this shift may be linked to the shift in muscle fibers characterized by an increase in glycolytic muscle fibers and a decrease in oxidative muscle fibers (69) (Figs. 1 and 2). Glycolytic fibers have lower rates of fat oxidation and lower insulin sensitivity compared with oxidative fibers, which have high mitochondrial density and oxidative enzyme activities. However, a study in rats showed that the shift in substrate use preceded the shift in muscle fiber type (24). Thus the mechanisms involved in these changes in substrate use are still poorly characterized. Some hypothesis can however be proposed on the changes in metabolic pathways.

Associated with the decreased muscle fat uptake, both human and rat studies showed that physical inactivity reduces gene expression of CPT-I (61) (Fig. 1), a protein responsible for the entrance of long-chain fatty acids into mitochondria. In addition of the altered fatty acid transport into myocyte and mitochondria, a reorganization of the metabolic pathways likely plays a role. Hindlimb suspension in rats for several weeks induces an increased glycolytic capacity in atrophied muscle (61, 72) via an increase in the gene expression of three key enzymes of glycolysis: hexokinase, phosphofructokinase, and kinase pyruvate (61). Conversely, a reduction in the capacity to oxidize lipids was indicated by a reduction in the gene expression of enzymes involved in the beta-oxidation (61).

Simultaneously to the changes in the glycolytic and oxidative pathways, a complementary hindlimb-tail rat study showed an increase in the gluconeogenic capacities of liver (62) that could explain the greater use of glucose by muscle. Another study using the wheel-locked model (53) also reported in the liver a lower mitochondrial oxidative capacity and a higher malonyl CoA concentration associated with increased levels of proteins involved in de novo lipogenesis, suggesting that similar alterations are occurring in liver and muscle. Based on these results, we can assume that the increase in glucose availability increases malonyl CoA concentration, which, by inhibition of the CPT-I, decreases the entrance of fatty acids into mitochondria, and hence fat oxidation. This results in an accumulation of nonoxidized fatty acids that are, in turn, likely synthesized as intramuscular lipids. An increase in gluconeogenic capacity has however still not been observed in humans (12) but remains to be demonstrated.

The intramuscular lipids can be in the form of triacylglycerol, diacylglycerol, and/or ceramides. A growing body of data showed that they contribute to alterations in insulin sensitivity. Although a negative correlation between intramyocellular triacylglycerol and insulin sensitivity has been repeatedly reported (31, 32), it is now accepted that it is not muscle triacylglycerol per se that induces insulin resistance but rather lipotoxic intermediaries such as diacylglycerol and ceramides (17, 30, 48). Although the respective role of these two intermediary lipids in insulin responsiveness alteration is still in debate, they are thought to engage stress-activated serine kinases that interfere with insulin signal transduction (28, 75).

PHYSICAL INACTIVITY INDUCES ECTOPIC FAT STORAGE

As expected, the reduced fat oxidation is observed concomitantly to different ectopic fat storages during bed rest (8, 20). For example, the significant increase in intramuscular lipid (+2.7%) observed after 2 mo of bed rest in healthy women (8) was correlated with the reduction in dietary palmitate oxidation (Fig. 1). This suggests that dietary fat is diverted from oxidation in muscle toward incorporation into muscle lipids. Along this line, the study of Settler et al. (65) showed an increase in intramuscular lipids with both high-carbohydrate and high-saturated-fat diets, but the increase was more marked after the high-saturated-fat diet (+32 vs. +17%). Although Settler et al. (65) did not observe a relationship between intramuscular lipid and insulin resistance likely due to the short period of the bed rest (2 days), Cree et al. (20) reported that intramuscular lipid negatively correlated with the reduced glucose uptake after 28 days of bed rest. The effects of physical inactivity on the different lipid fraction content, i.e., triglycerides, diacylglycerol, and ceramides, are still unknown. Studies investigating the profile of the intramuscular lipids are clearly required to better understand the relationship between the reduced oxidative capacity, the muscle fat storage, and the development of insulin resistance under physical inactivity conditions.

The accumulation of fat during bed rest seems to be a general phenomenon. It has indeed also been observed in bone marrow and within muscle fibers (71). Ectopic fat storage is thus likely to occur in other tissues. Although no direct measurements of fat in liver have been done in humans for obvious ethical reasons, suspended rats exhibit a lipogenic profile (53, 62), a reduced mitochondrial oxidative capacity, higher malonyl CoA concentrations (53), and an increase in gluconeogenic pathways (62). Altogether these results suggest the development of a nonalcoholic fatty liver. These aspects are further reviewed by Rector et al. (52a) as part of this Highlighted Topic series in the
Physical inactivity induces metabolic alterations

The data collected during bed rest showed strong evidence for an effect of physical inactivity on fuel homeostasis. The largest body of data from the literature certainly suggests that physical training improves metabolic flexibility. A key question thus emerged: Will the body response to a continuum of changes in physical activity levels linearly translate into changes in metabolic flexibility? To answer this question we combined two studies from our laboratories that studied flexibility over a wide range of physical activity levels. Briefly, we measured metabolic flexibility in active women and highly trained men before and after an intervention that markedly reduced their physical activity level (bed rest in women and detraining in men). Plasma insulin concentration and NPRQ (indirect calorimetry) were measured hourly before and after the consumption of two standardized meals. For each individual we used the insulin and NPRQ data to calculate the mathematical variance of the daily NPRQ and insulin responses to the test meals. From this, we calculated the average and the standard error of these variances per group. We defined metabolic flexibility by a low variance in insulinemia associated with an elevated variance in NPRQ, i.e., a small shift in the fuel mix being oxidized for a high insulin secretion, and the converse. By using this approach that placed subjects in normal physiological conditions, rather than in supraphysiological conditions as during a hyperinsulinemic euglycemic clamp, we showed that the variances of insulinemia and NPRQ are inversely but linearly associated along a physical activity continuum (Fig. 3). This indicates that habitual physical activity predicts metabolic flexibility.

CONCLUSION: A SCENARIO TO EXPLAIN HOW PHYSICAL INACTIVITY INDUCES METABOLIC INFLEXIBILITY

The review of the literature provides evidence that physical inactivity as investigated by bed rest induces, independently of measurable changes in energy balance, a reduced capacity to use fat as substrate, muscle atrophy, and a shift in muscle fiber type toward fast-twitch glycolytic type, a resistance to the effect of insulin and a hypertriglycerideremia along with an ectopic fat storage. Similar alterations in metabolic pathways are associated with metabolic disease state.

The following sequence of events can be hypothesized to explain the physical inactivity-induced metabolic alterations and thus metabolic inflexibility (Fig. 4). The physical inactivity induced by bed rest leads to insulin resistance in skeletal muscle, requiring a hyperinsulinemic response to properly dispose of glucose in daily postprandial conditions, whereas adipose tissue displays an appropriate response. At the same time, muscle fiber type shifts toward fast-twitch glycolytic fibers, and muscle increases glucose uptake and oxidation through insulin-independent pathways. This in turn inhibits fatty acid oxidation and ultimately uptake. During meal ingestion, hyperlipemia occurs due to a decreased plasma clearance of dietary fat. This increases the flux of dietary lipids to organs and results in ectopic fat storage with consequences on insulin sensitivity. The liver displays susceptibility to hyperinsulinemia and increased lipid synthesis and storage that overcomes rate of oxidations. Hepatic steatosis will likely ensue. With a reduced oxidative capacity, the liver will then contribute to an increased rate of atherogenic lipid products (VLDL) in which the contributions of FFA coming from the diet and neolipogenesis to the total VLDL-triglycerides will increase, feed-forwarding hyperlipemia and ectopic fat storage. Concomitantly, the steatotic liver will become insulin resistant and unable to suppress hepatic glucose production, which leads to increased gluconeogenesis and feed-forward worsening of hyperinsulinemia.

Although the hypothesis described above is plausible, the available data remain too scant to draw a more accurate kinetic
of the adaptations to bed rest. More controlled and standardized studies are needed to better assess the time course of changes. The present review presents other limitations. Most of the results reviewed therein were obtained in studies with small sample sizes (usually between 4 and 8) and mainly in male subjects. Some of the conclusions may not apply to women. It can also be difficult to have a good estimate of the decrease in physical activity experienced by the subjects since measurements of physical activity and total energy expenditure were not systematically done, even before bed rest. This critical piece of information is necessary to know if the observed effects stem from a decrease in physical activity, or from detraining in very active people/athletes, and consequently the extent to which the conclusions of a study can apply to the general population. Furthermore, numerous bed-rest studies, especially the earlier ones, did not tightly control the subjects’ diet, and the confounding effects of a potential positive energy balance should be kept in mind. In this present review, we finally did not mention one of the most important aspects of bed-rest studies: the countermeasures. The efficiency of pharmacological (e.g., pamidronate, resveratrol), nutritional (e.g., high-protein diet), and exercise (e.g., aerobic or resistive exercise training) countermeasures in alleviating the deleterious adaptations to space environment are tested in most bed rests. These results can provide valuable insight into the development of efficient strategies to counteract the effects of physical inactivity. Although these results are of great importance in the battle against the general adoption of sedentary behaviors, we chose to only focus our review on the negative effects of bed rest.

Despite these limitations, we believe that the data accumulated over years from the bed-rest studies support the idea that physical inactivity by itself is a main factor contributing to the onset of numerous chronic diseases. This again raises the importance of investigating directly the physiology of physical inactivity in order to better understand the impact of the adoption of sedentary behaviors in the general population on general health. Although bed rest is a unique model to investigate mechanisms underlying defects induced by physical inactivity in healthy subjects, it is important to remember that bed rest induces a level of physical inactivity likely different (quantitatively and qualitatively) from that observed in the general population. Studies that investigate the exact decrease in physical activity encountered over the past century in the general population will thus be needed to confirm these results. Future studies also need to determine the physical activity level threshold below which metabolic inflexibility is developed in order to refine the physical activity recommendations in the general population.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).
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