Overview of Glucose Metabolism and Aging

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Investigators interested in the effects of aging on glucose metabolism are faced with a difficult problem. The population of modern, wealthy nations are, to a large extent, sedentary and have food of high caloric density readily available to them. As a consequence, it is now usual for people to progressively gain weight with advancing age up to ~65 years of age. In a large proportion of individuals, much of this gain in fat is in the truncal and intraabdominal regions and is, to varying degrees, associated with the metabolic abnormalities of the abdominal obesity syndrome, including insulin resistance and, frequently, type 2 diabetes (3, 21). This pattern has now come to be thought of as due to aging (1, 2, 10, 11, 27, 28).

The use of rats and mice in laboratory studies of aging has further compounded this problem. As in the case of most humans living in the wealthy industrialized nations, “normal” laboratory rats or mice used to study the effect of “aging” on glucose metabolism are chronically sedentary, as they are housed in small cages. In addition, they are generally given unlimited access to food. As a consequence, they become obese (12, 18, 24). An additional problem is that there is great genetic variability in susceptibility to development of obesity and insulin resistance among individuals and between racial/ethnic groups in humans and between different strains of laboratory mice and rats.

What has been overlooked now is that being sedentary is a highly abnormal biological state. Throughout evolution, habitual vigorous exercise was necessary both to obtain food and to avoid being used for food. As a consequence we are not genetically adapted for a sedentary life, and the changes that occur with advancing age in sedentary individuals are partly due to aging per se and partly due to the consequences of exercise deficiency. Therefore, to determine the effects of normal aging, it is necessary to study humans or experimental animals that are habitually physically active.

Rats that are given access to voluntary wheels generally run long distances every night. The distance run varies from rat to rat within a species and from species to species. However, a ballpark average value for young rats is ~6 km/day with a progressive decline to 1.0–1.5 km/day by age 30 months (16–18). The voluntary runners do not become obese (9, 29). Similarly, rats made to swim for 3 hours/day, 5 days per week, gain much less weight with advancing age than sedentary rats, despite free access to food (12). Rats exercised by swimming showed no decline in insulin stimulated muscle glucose uptake between 9 and 24 months of age, and had significantly higher rates of muscle glucose uptake than sedentary rats of the same age (19).
The abdominal obesity syndrome consists of central obesity with a large amount of intraabdominal (visceral) fat, insulin resistance, hyperglycemia, and hyperlipidemia (4, 5, 21). This syndrome frequently progresses to type 2 diabetes (4, 5, 21). It is the result of the interaction between the genotypes(s) for insulin resistance and prolonged positive energy balance. Obesity is not seen in stone age hunting-gathering societies or in subsistence farmers. However, the genotype(s) responsible for the abdominal obesity syndrome must occur with high frequency in such populations, because obesity and type 2 diabetes have attained near epidemic proportions in ethnic groups that have recently converted from a hunter-gatherer to a sedentary, modern lifestyle. Such groups include American Indians, Australian aborigines, and Polynesians (23, 30, 31).

The abdominal obesity syndrome is generally thought to be caused by overeating, and the high incidence of obesity and type 2 diabetes in these ethnic groups is frequently attributed to the increased availability and consumption of food of high caloric density. This is a misconception. Hunter-gatherers, both men and women, expend large amounts of energy obtaining food and frequently moving from one campsite to another. Their caloric intakes are comparable to those of athletes in modern societies. An example are the Ache, a tribe living under essentially stone age conditions in the tropical rain forest of Paraguay. The Ache men consumed ~3700 kcal/day, of which approximately 56% came from monkey meat, ~18% from honey, and 26% from plants and insects (15). By comparison, obese (>149% optimal weight) middle-aged men in the U.S. have an average caloric intake of ~2300 kcal/day, and for overweight middle-aged women, the value is ~1500 kcal/day (6).

The energy intakes of sedentary middle-aged obese people in wealthy modern societies are ~200–400 kcal/day less than those of young people (6, 13, 22), so the weight gained with increasing age is due to physical inactivity rather than to an increase in food intake—that is, to the abnormal condition of a sedentary lifestyle. A gain in body weight of 28 kg between ages 25 and 50 years requires an excess energy intake of only ~25 kcal/day. The biological mechanisms that regulate appetite are not sufficiently fine-tuned to correct for such a small variations in caloric intake. In contrast, individuals who have a high daily energy expenditure tend to maintain their body weight relatively constant into late middle age.

In this context, it seem obvious that in order to obtain information on the effect on aging per se on glucose metabolism, it is necessary to study normal aging which, because we are not genetically adapted for a sedentary life, only occurs in individuals who exercise regularly. Jobs that require vigorous physical activity have become rare in modern society. Furthermore, those individuals who do still have physically demanding occupations frequently come from a low socioeconomic background and have poor health habits (i.e., smoking, bad diet, high alcohol intake, etc.). Thus, it has become necessary to study individuals who exercise regularly during their leisure time on a year around basis. Probably the only such individuals are master athletes and the few people who exercise as faithfully as master athletes but do not compete.

In healthy sedentary individuals in our society there is, on average, a progressive deterioration in glucose tolerance, with higher plasma levels of both glucose and insulin at each time point of the glucose tolerance test with advancing age up to ~75 years (14). There is also a progressive increase in the percentage of individuals with impaired glucose tolerance and type 2 diabetes. There is also a
small subgroup of individuals who stay relatively lean and develop impaired glucose tolerance or diabetes as the result of insulin deficiency. This insulin deficiency syndrome is poorly understood and its cause is not known. However, in the great majority of people, increasing insulin resistance due to development of abdominal obesity is responsible for the deterioration of glucose tolerance with advancing age (7, 8, 20).

Because development of obesity is preventable and not a part of normal aging, it seems reasonable that development of insulin resistance and deterioration of glucose tolerance with advancing age in the U.S. and other sedentary societies is, to a large extent, not due to aging per se. Two lines of evidence support this conclusion. One is that even in the oldest age group, there are some individuals whose plasma glucose and insulin responses to an oral glucose tolerance test (OGTT) are similar to those of lean, healthy young people (Figure 1). Admittedly, the percent of sedentary individuals with such “strictly normal” OGTTs decreases dramatically with advancing age, with only ~10% of sedentary 80–90 year olds having strictly normal glucose tolerance. However, aging is a universal phenomenon that affects everyone. For example, no one is spared the development of presbyopia, or the

Figure 1 — Plasma glucose and insulin concentrations during a 75-g oral glucose tolerance test (OGTT) for 54 young, lean, healthy subjects (20–30 years) and 6 old men and women (78–94 years) with a strictly normal (i.e., young) response to the OGTT.
inexorable declines in \( \dot{V}O_2 \)max, renal function, or pulmonary function. Thus, if the decline in insulin action and glucose tolerance were due to aging, there should be no octogenarians with strictly normal OGT, in the same way as there are no individuals in their 80s who have \( \dot{V}O_2 \)max values of 60 ml/kg/min or who have not developed presbyopia.

The second line of evidence that the large declines in glucose tolerance due to development of insulin resistance with advancing age in sedentary individuals in the U.S. are not primarily due to the aging process comes from the small amount of data available on master athletes. In one study, a group of 14 endurance trained master athletes aged 60 ± 7 years had plasma glucose responses to an OGTT that were the same as those of young athletes and young sedentary men (26). The area above fasting baseline under the glucose curve during the OGTT was ~50% as great for the master athletes and young groups as for healthy sedentary men who had good glucose tolerance for sedentary 60-year-old men. The insulin secretory response is blunted in trained individuals, and the area above baseline under the insulin curve during the OGTT was ~50% lower in both the young and the older athletes than in the young untrained men (26). The most remarkable findings of this study were that (a) glucose tolerance and insulin action were as good in the master athletes as in the
young athletes who were 34 years younger, and (b) the master athletes cleared a 100-g glucose load as rapidly as young untrained subjects despite ~50% lower insulin levels. In another study involving 14 master athletes aged 61 ± 8 years, the plasma glucose response to a 100-g OGTT was not significantly different from that of young athletes or young untrained men (25). In contrast to the master athletes in the first study (26), this group of master athletes had a larger insulin response to the OGTT than the young athletes; however, their insulin response (i.e., area under the curve) was significantly lower than that of the young untrained subjects (25).

The findings on these 28 master athletes provide evidence that normal aging (i.e., in people who exercise regularly) does not result in an appreciable deterioration in glucose tolerance or insulin action at least up to age ~70 years. Since normal aging does result in a progressive deterioration in structure and function of all tissues, one would have to be a Pollyanna to conclude that aging does not result in some deterioration in glucose tolerance due to aging per se. However, the major factor in the development of insulin resistance and the deterioration in glucose tolerance with advancing age appears to be a sedentary lifestyle that results in abdominal obesity.

References


