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Guest Editorial

Insulin Resistance and Aging: A Cause or a Protective Response?

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If you are bitter at heart, sugar in the mouth will not help you.
Traditional Yiddish Proverb

METABOLIC syndrome consists of metabolic defects associated with increased risks of type 2 diabetes mellitus, cardiovascular diseases, prothrombotic and inflammatory states, and possibly Alzheimer's disease, cancer, and reduced longevity (1). The metabolic syndrome of aging was originally called *insulin resistance syndrome*, pointing to insulin resistance as the key factor. In older persons, age-related rise of visceral adiposity and accumulation of senescent cells with inflammatory phenotype result in high blood levels of proinflammatory cytokines that likely interfere with insulin signaling (2). The resulting insulin resistance is characterized by dysfunctional IRS–PI3–kinase/Akt pathway that causes impaired glucose uptake in muscle and fat cells, reduced glycogen synthesis/storage in the liver, and failure to suppress hepatic glucose production. Insulin resistance contribute to increase cardiovascular morbidity in part through impairments in lipid uptake and storage of circulating lipids leading to increased plasma levels of *very low-density lipoprotein* (proatherogenic apoB-containing/triglyceride-rich lipoproteins),which is typical to this syndrome (1). Because of its high prevalence and strong association with many adverse outcomes, insulin resistance is often considered having a causal role in many adverse aging phenotypes and age-related conditions. In fact, it has even been suggested that counteracting insulin resistance could be an effective "antiaging" intervention. This view is in open contrast with widely accepted notion that a downregulation (by genetic modulation) of the insulin signaling pathway in invertebrates is associated with exceptional longevity (3). In fact, over the last decade, the search for the mechanisms by which decline in insulin action leads to longevity has been the most frequent and productive research topics in the biology of aging.

The first explanation that comes into mind for this paradox is that mammalian physiology is several orders more complex than invertebrate and the role of insulin signaling has evolved to encompass regulatory functions beyond carbohydrate handling. Hence, the relationship of insulin signaling dysregulation and longevity is quite different across species. Genetic modifications that downregulate the entire insulin signaling may have different effects than insulin resistance where only some specific insulin actions are impaired. There is no doubt that the overproduction of insulin from the pancreas partially and temporarily counteracts the effects of insulin resistance on glucose and lipids. However, high insulin levels also result in activation of the mitogen-activated protein kinase pathways, which is not affected by insulin resistance and stimulates cellular migration, vascular smooth muscle cell proliferation, and a prothrombotic state. Thus, the compensatory hyperinsulinemia can progressively shift the balance of insulin signaling toward a mitogenic state leading to accelerated atherosclerosis.

Indeed, euglycemic clamp studies in caloric-restricted animals (4–6) revealed enhanced insulin sensitivity compared with normally fed controls (7–9). Surgical removal of visceral fat in aging rodents restored insulin sensitivity and prolonged life span (10). Administration of resveratrol, a compound that activates sirtuin (sirtuin molecules have been associated with longevity), to aging mice on a high-calorie diet increases insulin sensitivity and normalizes their life span (11). However, there is also evidence that insulin sensitivity and longevity may lie on different causal pathways that are not necessarily interconnected. Signaling downregulation of the target for rapamycin and more

Table 1. Examples from Intervention in Rodent Models Supporting Lack of Association between Insulin Sensitivity and Longevity

Examples for decrease insulin sensitivity but with increased longevity:
IRKO+/– (13)
IR ($IrP^{1195}L$/wt) (14)
IRS2+/– (15)
IRS2+/– in brain (15)
IRS1–/– (16)
Klotho transgenic mice (17)
Rapamycin-treated mice (18)
Examples increased insulin sensitivity with decreased or unchanged longevity:
PTP1B knockout mice (13)
PGC1—a transgenic mice (13)
Resveratrol-treated mice (without high fat diet) (19)
Glut4 transgenic mice (20)
Metformin-treated rats (21)

recently of its mammalian equivalent extends life spans in multiple species, by multiple mechanisms such as enhanced autophagy and decreased mitochondrial production of reactive oxygen species. Interestingly, reduction of mTOR signaling is associated with decreased insulin sensitivity (12). In this special issue of *Journals of Gerontology: Biological and Medical Sciences* (13), Nelson and his colleagues present data on insulin sensitivity in three rodent models that were primarily studied for longevity. Although the insulin-resistant model (IRKO+/–) lived longer, two insulin-sensitive models (PTP-1B–/– or PCG-1αTG) tended to have shorter middle or maximal life span. These data suggest that in mammals, enhanced insulin sensitivity is neither a necessary nor a sufficient step toward increased longevity. Table 1 includes other examples where longevity and insulin sensitivity were separated (14–21). Such a paradoxical window of the relationship between insulin signaling and longevity across species clearly casts serious doubts on whether downregulating the insulin signaling may have beneficial effects in humans. Haven't we always been told that insulin resistance is "evil" and should be prevented and fought in any possible way? In reexamining the role of insulin resistance in human aging and life span, it is important to realize that insulin resistance is just one of the effects of central obesity, in addition to hypertension, hyperlipidemia, and other elements of the metabolic syndrome. Selective improvement of insulin sensitivity is unlikely to reverse other features of the metabolic syndrome, and evidence for the notion that increasing insulin sensitivity reduces cardiovascular morbidity and mortality is limited. Because insulin resistance is an evolutionary conserved mechanism, one possible solution to this conundrum is that while insulin resistance is associated with harmful effects, it is also a primarily protective mechanism against some dangerous threat to life homeostasis. Mechanistically, decreased insulin signaling is linked in many invertebrate studies to regulation of stress response (22). In mammalians, in the face of increased nutrient availability, insulin resistance may be necessary to limit glucose uptake in muscle cells where glycogen and lipid stores are already saturated. Indeed, further "fuel" provision to muscle mitochondria may clutter an already dysfunctional electron transportation chain and increase reactive oxygen species production that could be viewed as a powerful antioxidant mechanism (23), and as discussed more by Nelson et al. (13). This may explain why insulin resistance has been so prominent evolutionary in the longevity of many models. If enhanced defense mechanisms contribute to increased longevity of invertebrates with reduced insulin signaling, it is possible to imagine that pharmacological reduction of insulin resistance by drugs in humans may impair defense mechanisms. Although decreasing insulin resistance is a major strategy to relieve some demands on pancreatic beta cells to increase insulin secretion in type 2 diabetes mellitus, it may be associated with less protection of other organs. Insulin-sensitizing thioglitazones, which are nuclear peroxisome proliferator-activated receptor gamma activators, are very effective in treating hyperglycemia of diabetes and preventing some of its vascular complications, yet one could argue that removing the defense of insulin resistance may have contributed to more cardiovascular diseases observed in some studies (24) in spite of improvement in glucose levels. Thus, although insulin sensitivity is essential for normal functioning of the organism and its enhancement may extend longevity, insulin resistance in aging humans may play an adaptive role. Given these premises, the search for the meaning of insulin resistance and its importance for longevity will not stop any time soon.

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