Insulin signaling in peripheral tissues entails activation of the insulin receptor substrate (IRS)-phosphatidylinositol 3-kinase (PI3K) enzyme system. In the hypothalamus, insulin functions with leptin as an afferent adiposity signal that is important for the regulation of body fat stores and hepatic glucose metabolism. Studies have shown that the IRS-PI3K pathway is a mediator of insulin action in the arcuate nucleus as well. Combined with recent evidence that leptin activates PI3K signaling in the hypothalamus, this suggests a conduit for neuronal crosstalk between insulin and leptin signaling (Niswender et al. *Diabetes* 2003).

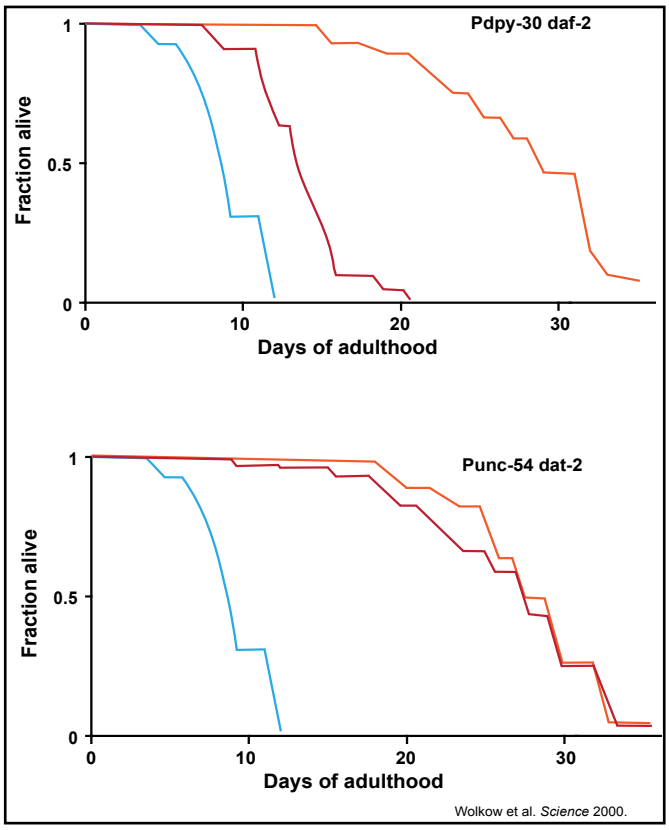
Mice that lack IR have proven to be invaluable in gaining a better understanding of the role of insulin action in the brain. Downregulation of neuronal IR expression results in severe hyperinsulinemia and a dramatic upregulation of hepatic leptin receptor expression. Leptin replacement restored normal glucose metabolism in these mice. Insulin action, specifically in AgRP-expressing neurons, does play a critical role in controlling hepatic glucose production and may provide a target for the treatment of insulin resistance in type 2 diabetes (Koch et al. *JCI* 2008; Konner et al. *Cell Metab* 2007).

Caloric restriction has been strongly associated with a reduction in aging-associated pathologies, thereby resulting in a longer, healthier life. As first demonstrated in *Drosophila* (Chapman et al. *Proc Roy Soc* 1996), and later in *C. elegans* and mice, it is clear that restricted caloric intake can increase longevity.

Selman et al. were able to localize this benefit to the CNS, observing that IRS-1-deficient mice stay healthy and disease-free longer and had the ability to maintain glucose homeostasis (FASEB 2008). This work was replicated in *C. elegans*, verifying that the nervous system's relationship with insulin is a central regulator of animal longevity (Wolkow et al. *Science* 2000; Figure 2).

The residence of such activity in the CNS raises a question about whether glucose dysregulation plays a role in age-related diseases of the brain, such as Alzheimer disease (AD). An animal model of AD was shown to have downregulated IGF-1R and IR and an excessive presence of their key substrate adaptor proteins, IRS-1 and IRS-2, the physiological equivalent of insulin resistance. The increase in IGF-1R was detected around and within amyloid beta-containing plaques, the pathological hallmark of AD, and resistant to IGF-1R/IR signaling (Moloney et al. *Neurobiol Aging* 2008); yet, this link is merely hypothesis-generating. One recent study by Moroz et al. assessed AD-type neurodegeneration in a type 2 diabetes mellitus (T2DM) mouse model but did not observe an AD histopathology, leading the authors to conclude that obesity and T2DM may contribute, but are not sufficient, to cause AD (Moroz et al. *J Alzheimer's Disease* 2008).

Figure 2. Restoring IIS in the CNS Abrogates the Life-Extending Effect of Systemic IR in *C elegans*.



The physiological importance of this homeostatic control system is highlighted by the severe obesity that results from the dysfunction of any of its key components. This new information provides a biological context within which to consider the global obesity epidemic and identifies numerous potential avenues for therapeutic intervention and future research (Schwartz et al. *Nature* 2006).

Insulin Resistance as a Major Risk Factor for Cardiovascular Disease

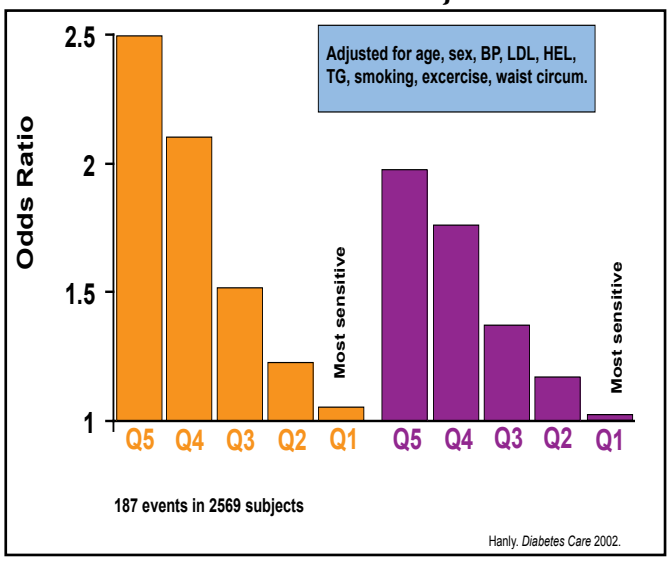
Insulin resistance is emerging as a major contributor to cardiovascular risk, and the lipotoxicity that is associated with obesity is a key factor in the development of insulin resistance (IR). Recent data that suggest that thiazolidinediones (TZDs) may provide some insight into this issue were reviewed by Ralph A. DeFronzo, MD, University of Texas Health Science Center, San Antonio, TX.

Insulin resistance is a characteristic of type 2 diabetes mellitus (T2DM) and all components of the metabolic syndrome. Macrovascular disease (myocardial infarction [MI], stroke) accounts for 80% of all mortality in T2DM. So, how large a role does hyperglycemia play in the pathogenesis of atherosclerosis in diabetic subjects, and does glycemic control alone improve cardiovascular disease (CVD) outcome?

A report from the UK Prospective Diabetes Study showed a 37% reduction in microvascular events (retinopathy, neuropathy), a 12% decrease in stroke, and a 14% reduction in MI per 1% reduction in HbA1c levels (Stratton. *BMJ* 2000). However, these results have not been replicated in the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) or the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trials. This result may be explained by an incorrect hypothesis, the wrong patient population (already exhibiting cardiovascular damage due to long-term diabetes), or an inadequate sample size. In order to sufficiently power a trial that could determine if glycemic control alone reduces CVD risk, approximately 6800 patients would be required to participate in a 10-year study.

Despite this lack of direct evidence, multiple prospective epidemiological studies have demonstrated that both IR and the metabolic syndrome are predictive of CVD as well as future diabetes onset. In the San Antonio Heart Study (SAHS), after adjusting for age, gender, high cholesterol, and smoking status, IR is indicated as a predictor of CVD development in nondiabetic patients at an 8-year follow-up (Hanly et al. *Diabetes Care* 2002; Figure 1).

Figure 1. Association Between HOMA-IR and 8-Year Incidence of CVD in Nondiabetic Subjects in SAHS.



Data from numerous laboratories recently have elucidated the pathways that account for IR and its impact on CVD risk. In brief, insulin receptor substrate-1 (IRS-1) is the initial transmitter of the insulin signal at the cell membrane. Once it is activated, this molecule can then go on to promote not only glucose metabolism but also vasodilation via the PI-3 kinase pathway. Alternately, under conditions of IR, IRS-1 can induce MAP kinase activation, leading to the inflammation that is characteristic of the formation of atherosclerosis (Mandarino et al. *Diabetes* 2003).

Given the dual nature of IRS-1 signaling, it is not feasible to block its activity with a drug – the loss of the PI-3 pathway would negate any benefit that is derived from shutting down MAP kinase. However, the TZD drug class hits both targets and is able to stem inflammation that is caused by IR while at the same time facilitate arterial well-being via PI-3 kinase/NOS signaling (Figure 2; DeFronzo et al. *Diabetes* 2003).

The TZDs also can address lipotoxicity, a factor that also is shown to drive CVD risk (Kashyap *Diabetes* 2003). Operating through the NF-kappa B pathway, free fatty acids (FFAs) induce inflammatory cytokines while at the same time downregulate the beneficial PI-3 pathway. In several studies of TZD, pioglitazone has been shown to reduce FFA and reduce cardiovascular events in T2DM subjects (PROactive Investigators. *Lancet* 2005). There also is evidence to show that pioglitazone halts the progression of atherosclerosis (Nissen. *JAMA* 2008).

Together, these observations argue for a greater emphasis on the treatment of IR and the management of prediabetic obese patients.

Figure 2. Insulin Signal Transduction System in T2DM Humans: Effect of TZDs.