Palmitate also induces IRE1 signaling, promoting cell survival through downstream chaperone activation or, alternately, tipping the scales toward apoptosis through activation of Jun kinase (JNK). This association was shown using JNK inhibitors. In vitro work also was able to verify the palmitate/UPR/CHOP association by knocking down palmitate-induced expression with the use of CHOP siRNA and thus partially protecting beta-cells against palmitate-induced apoptosis (Cunha et al. *J Cell Sci* 2008).

Conversely, IRE1 signaling that promotes cell survival through the production of chaperones (eg, BiP) was validated through the use of BiP overexpression to rescue an insulin-secreting cell line from lipid-induced apoptosis (Laybutt et al. *Diabetologia* 2007).

A final association is to be made between ER stress and the dysfunction and loss of beta-cells, as seen in diabetes. Studies have shown that in the islets of db/db (diabetic) mice, numerous ER stress factors were unregulated – this also is true of human islet preparations (Laybutt et al. *Diabetologia* 2007). More to the point, both the proapoptotic CHOP expression and the ER area were increased in islets from patients with T2DM (Huang et al. *Diabetes* 2007; Marchetti et al *Diabetologia* 2007). Interestingly, islets from obese patients also show some increase in cytosolic CHOP expression. This, and additional evidence, suggests that ER stress may be a common mediator of both beta-cell death and insulin resistance in T2DM (Eizirik et al. *Endocrine Reviews* 2008).

KIOM-79 Slows the Development of Diabetic Retinopathy in Animal Models

Treatment with KIOM-79, a novel mixture of 4 herbal extracts, appears to slow the development of retinopathy, according to a new animal study of diabetic eye disease. In addition to characterizing the treatment effects of KIOM-79, the study provides important insights into the pathophysiology of diabetic retinopathy.

Vascular Damage in Retinopathy

Researchers have previously observed the accumulation of advanced glycation end products (AGEs) in the neural retina and vascular cells of diabetic animals (Miura J et al. *J Diabetes Complications* 2003). In these animals, AGE accumulation appears to induce the programmed death of retinal pericytes and neuronal cells. Retinal pericyte apoptosis leads to a range of damaging events within the retina, including the development of microaneurysms, retinal hemorrhages, neovascularization, and permanent impairment of visual function.

KIOM-79 contains the extracts of 4 herbs: parched *Puerariae radix* and gingered *Magnoliae cortex, Glycyrrhizae radix*, and *Euphorbiae radix*. These agents inhibit AGE-induced apoptosis by preventing NFkB activation and lowering proapoptotic cytokine production. Jin Sook Kim, MD, Korea Institute of Oriental Medicine, Daejeon, Republic of Korea, described the effects of KIOM-79 on AGE-induced retinal damage.

Treatment Effects of KIOM-79

In the current study, Dr. Kim and colleagues treated 7-week-old male Zucker Diabetic Fatty (ZDF) rats with KIOM-79 (50 mg/kg) or placebo once daily for 13 weeks. Normal, untreated rats also were included as control animals. At the end of the treatment period, the retinas were harvested and examined for signs of vascular damage.

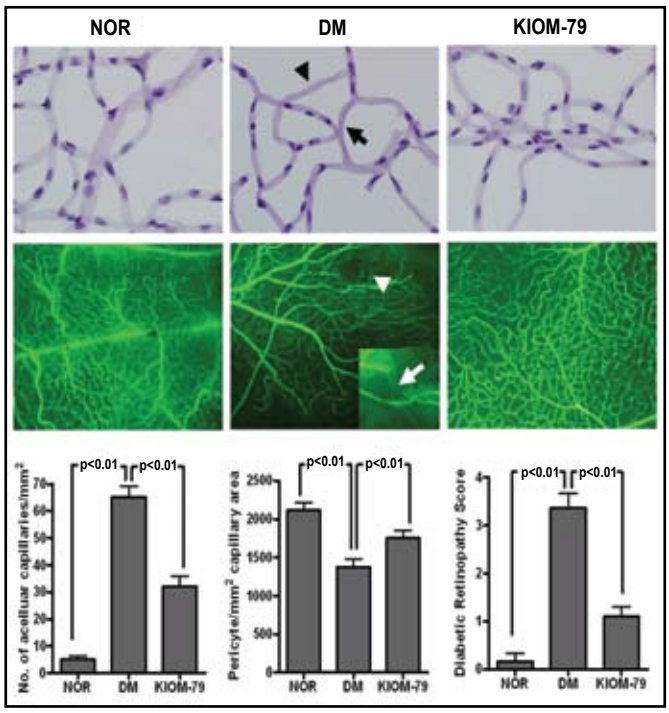
Compared with rats in the vehicle-treated group, KIOM-79-treated rats had significantly lower serum levels of AGEs ($p<0.05$) and lower numbers of AGE-positive retinal cells ($p<0.05$).

Retinas from the vehicle-treated group showed evidence of vascular damage when assessed by immunohistochemistry, including areas of retinal pericyte loss and the appearance of acellular capillaries. However, these vascular changes rarely were observed among retinas that were harvested from KIOM-79-treated rats (Figure 1, top panel).

Additional fluorescein staining allowed researchers to calculate retinal angiography lesion scores, which are an indication of the degree of retinopathy. When assessed by fluorescein staining, retinas from vehicle-treated ZDF rats showed severe signs of vascular damage, including vessel-narrowing, fluorescein leakage, and nonperfusion of fluorescein. By contrast, retinas from KIOM-79-treated diabetic rats showed significantly fewer changes in retinal angiography ($p<0.05$; Figure 1, middle panel).

These findings provide quantitative evidence to support the further study of KIOM-79, Dr. Kim said. "Treatment with KIOM-79 is useful in inhibiting the accumulation of AGEs in retinal tissue and has a preventive effect on the development of diabetic retinopathy," she concluded.

Figure 1. Effects of KIOM-79 on Retinal Vascular Damage.



Top panel: Immunohistochemistry of retinal samples showing pericyte ghost (arrow) and acellular capillary (arrowhead).

Middle panel: Fluorescein angiography showing nonperfusion areas and vessel-narrowing (magnified inset).

Bottom panel: Quantitative analysis of acellular formation, pericyte ghosts, and retinopathy score of retinal vessels. Nor = normal, untreated rat; DM = ZDF rat treated with placebo; KIOM-79 = ZDF rat treated with KIOM-79.

Insulin Signaling, the CNS, and Longevity

Numerous recent studies of animal models suggest a highly active role for the central nervous system (CNS) in energy homeostasis. While this is not surprising, an expansion of these findings indicates that insulin signaling has a pronounced influence on the lifespan of a wide array of organisms. Jens Claus Brüning, MD, University of Cologne, Cologne, Germany, and winner of the 2008 Oskar Minkowski Prize, discussed these data in the 43rd Minkowski Lecture.

To the frustration of some researchers, insulin has been shown to have pleiotropic effects in nearly all tissues. Yet to date, the primary focus of these investigations has been on insulin activity in the peripheral tissues. Indeed, for many years insulin also was the primary hormone, or signaling molecule under consideration, but there was a paradigm shift in the understanding of metabolic regulation with the discovery and eventual isolation of leptin.

Leptin created a sensation in the lay press as well as in the peer-reviewed literature, because its activity in the body affected feeding behavior. Mice with defective leptin expression were observed to be obese (Shang et al. *Nature* 1994). Leptin deficiency in humans also was identified and fueled the assumption that the cause of obesity had indeed been found. Although patients did respond dramatically to leptin augmentation, the underlying hormonal defect was determined to be fairly rare. Research then shifted in perspective to consider not only the signal, but also the receiver. Leptin that is produced in adipose tissue has been shown to bind to the ventromedial nucleus of the hypothalamus, the center of appetite control. The message that is carried by this diminutive 16-kD protein is that the body has met its energy requirements, stimulating the brain to send signals to the body to stop eating.

This activity was further localized to the ARC (hypothalamic arcuate nucleus) neurons, and thereafter multiple signals were identified as being targeted to this area. These included leptin, insulin, GLP-1, and glucose (Figure 1). The focus on ARC neurons was further validated by murine investigations, showing that if agouti-related peptide and neuropeptide Y, normally expressed in ARC, were disabled, feeding behavior was unaltered. However, if the neurons that expressed these genes were themselves ablated, food intake was drastically reduced, nearly to the point of starvation. ARC neurons are now known to play a critical role in the regulation of energy homeostasis (Gropp et al. *Nat Neuro* 2005).

Figure 1. ARC Neurons as Targets of Multiple Signals.