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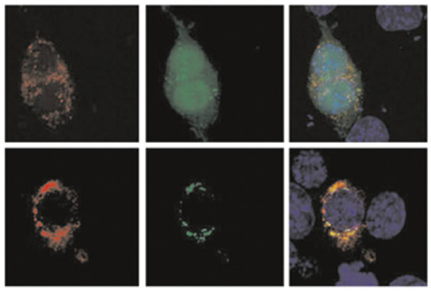
In This Issue of *Diabetes*

Edited by Helaine E. Resnick, PhD, MPH

New Insight on Heat Shock Protein 72 in Metabolic Disease

A new study in this issue of *Diabetes* (**p. 1488**) suggests that preservation of heat shock protein 72 (HSP72) may offer meaningful opportunities to develop novel therapeutic strategies for metabolic conditions like diabetes. Although the heat shock response is highly conserved across species and deficiencies in this process are associated with shorter life expectancy, the mechanisms behind these processes have been poorly understood. The study builds on previous work that showed experimentally elevated HSP72 was protective against obesity and insulin resistance, which were induced by both diet and leptin deficiency. Although the previous findings suggest a strong association between lower levels of HSP72 and metabolic disease, the work did not demonstrate causality. In the new report, Drew et al. demonstrate that HSP72 translocates to the mitochondria where it regulates Parkin, a protein that is critical for mitochondrial quality control. A series of experiments that compares HSP72 knockout and wild-type mice shows that the absence of HSP72 results in insulin resistance and obesity, as well as defects in myocytes that are related to insulin action and the handling of fatty acids. Additional experiments not only demonstrate that HSP72 is critical for appropriate Parkin protein and autophagic signaling, but that HSP72 also regulates the abundance of Parkin protein. Moreover, the new experiments suggest that HSP72 is a required element for the regulation of Parkin protein and that, in turn, Parkin is associated with insulin action in muscle. The potential long-range implications of these findings focus on the idea that therapies aimed at increasing HSP72 in muscle may favorably impact oxidative damage, inflammation, and insulin resistance, all of which are central features of metabolic disease, including diabetes. — *Helaine E. Resnick, PhD, MPH*



HSP72 translocates to damaged mitochondria and regulates Parkin-mediated mitophagic signaling.

Drew et al. HSP72 is a mitochondrial stress sensor critical for Parkin action, oxidative metabolism, and insulin sensitivity in skeletal muscle. Diabetes 2014;63:1488–1505

Hypoglycemia Is Linked to Arrhythmias in Type 2 Diabetes

What links aggressive glucose control and increased mortality? An intriguing article in this issue of *Diabetes* (**p. 1738**) may help explain this troubling observation. Despite the established benefits of intensive glucose control on microvascular outcomes, similar effects have not been systematically observed for cardiovascular and all-cause mortality. In some instances–such as the ACCORD trial–tight glucose control was associated with elevated mortality among people with type 2 diabetes who were at high risk of cardiovascular disease (CVD). Although the results of the ACCORD study have been discussed at length, the mechanism or mechanisms explaining elevated mortality risk among high-risk type 2 diabetic patients remains elusive. The new study by Chow et al. suggests that hypoglycemia, often an unfavorable consequence of tight glucose control, is associated with arrhythmias in people with type 2 diabetes who are at high risk of CVD. The study summarizes extensive data from 25 people with type 2 diabetes whose clinical profiles closely reflect those of participants in the ACCORD trial. As they carried on with routine activities, participants had simultaneous Holter monitoring and interstitial glucose monitoring. There were 2,323 h of data collected, of which 134 h were in hypoglycemia, 65 h were in hyperglycemia, and 1,258 h were spent in euglycemia. Among the key findings in the new report was the observation that relative to euglycemia, bradycardia was eight times higher during nighttime hypoglycemia and, when hypoglycemia occurred, arrhythmias occurred more frequently at night. These new data suggest that hypoglycemia is proarrhythmic and may explain previous observations concerning increased mortality risk among intensively treated diabetic patients at high risk of developing CVD. — *Helaine E. Resnick, PhD, MPH*

Chow et al. Risk of cardiac arrhythmias during hypoglycemia in patients with type 2 diabetes and cardiovascular risk. Diabetes 2014;63:1738–1747

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Promising Results for Insulin Analog That Targets Liver

New data suggest that proinsulin-transferrin (ProINS-Tf) fusion protein may hold promise as a long-acting insulin analog that specifically targets the liver. The authors of the new study in this issue of *Diabetes* (**p. 1779**) built on their previous work, which converted a ProINS-Tf recombinant fusion protein to an active form of insulin-transferrin (INS-Tf). In a new series of experiments in mice, Wang et al. show that ProINS-Tf has a sustained hypoglycemic effect that was achieved through inhibition of hepatic glucose production. The relevance of this work lies not only in the possibility of developing a new insulin analogue, but one that is a long-acting agent that targets the liver. The importance of this work is further highlighted when considering the basic features of insulin action: Insulin lowers blood glucose by increasing peripheral insulin disposal and by lower hepatic glucose output. The authors point out that under normal conditions, the pancreas sends insulin directly into the portal vein where about 50% is cleared before the insulin reaches muscle and fat in the periphery. The liver is therefore exposed to 2–4 times higher insulin levels than peripheral tissues, a feature that allows insulin to have a greater impact on hepatic glucose reduction than on glucose disposal in muscle and fat. It is against this backdrop that ProINS-Tf's prolonged pharmacokinetics and duration of preferential action on the liver are of the greatest potential importance for the development of novel agents for treating hyperglycemia. — *Helaine E. Resnick, PhD, MPH*

Wang et al. Proinsulin-transferrin fusion protein as a novel long-acting insulin analog for the inhibition of hepatic glucose production. Diabetes 2014;63:1779–1788

New Insight on Liver and Gut After RYGB

It is well established that Roux-en-Y gastric bypass (RYGB) surgery results in marked decreases in body weight and improvements in glucose metabolism, but the mechanisms underpinning postsurgical improvements in insulin sensitivity and insulin secretion remain poorly understood. An article in this issue of *Diabetes* (**p. 1725**) focuses on 20 obese patients who underwent RYGB surgery. In addition to their obesity, 10 of the 20 patients also had diabetes while the other 10 had normal glucose tolerance. Patients were studied before RYGB surgery as well as at 1 week, 3 months, and 1 year after surgery. Bojsen-Møller et al. used clamp techniques and both oral and intravenous glucose challenges to assess a variety of parameters including insulin sensitivity, insulin clearance, and β-cell function. At 1 week after surgery, patients in both groups showed improvements in all three parameters, an observation that supports an important role for the liver in the short-term improvements in glucose metabolism after surgery. Although glucose disposal did not improve immediately, beneficial effects were observed at 3 months and 1 year after surgery, a finding that the investigators attribute to postsurgical weight loss. One of the most interesting findings in the new report is that insulin secretion improved only in the patients with type 2 diabetes, and these improvements were only observed in response to an oral (vs. intravenous) glucose challenge. These intriguing observations indicate that the gut plays a critical role in the observed improvements in glucose metabolism after RYGB. — *Helaine E. Resnick, PhD, MPH*

Bojsen-Møller et al. Early enhancements of hepatic and later of peripheral insulin sensitivity combined with increased postprandial insulin secretion contribute to improved glycemic control after Roux-en-Y gastric bypass. Diabetes 2014;63:1725–1737

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