Kidney News

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New Clue to Diabetic Nephropathy?
Podocyte Protein Linked to Hyperglycemia-Induced Kidney Damage in Mouse Model

By Tim O’Brien

Deficiency of protein tyrosine phosphatase 1B (PTP1B), specifically in podocytes, protects against hyperglycemia-induced renal damage in mice, according to a recent study in Metabolism.

The experimental study provides a tantalizing clue to the molecular mechanisms by which podocyte dysfunction leads to diabetic nephropathy—one of the most devastating complications of diabetes.

“We provide evidence of increased PTP1B expression in podocytes under high glucose,” according to the research by Fawaz G. Haj, MSc, DPhil, of the University of California, Davis, and colleagues. “Also, podocyte-specific PTP1B disruption attenuated hyperglycemia-induced renal injury and preserved glucose control.”

Haj and his colleagues performed a series of experiments to clarify the role of PTP1B in renal function. Previous

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In Wake of Opioid Epidemic, Nephrologists Aim to Balance Pain Control, Safety in Patients

By Bridget M. Kuehn

More than 60% of dialysis patients had one or more prescriptions for a short course of opioid medications each year between 2006 and 2010, according to a recent analysis by scientists from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). About 20% of these patients had a prescription for a supply of 90 days or more of these medications.

The analysis, which used information from the U.S. Renal Data System on about 300,000 patients receiving dialysis with Medicare coverage, also found that both short-term and long-term use of opioids was associated with worse patient outcomes, including increased mortality, dialysis discontinuation, and hospitalization, according to lead author Paul Kimmel, MD, program director in NIDDK’s Division of Kidney, Urologic, and Hematologic Diseases, and his colleagues.

“The only question is, are these drugs causing [poor outcomes] or are they a marker for poor health,” Kimmel said in an interview. “Are patients who are sicker having more pain?”

The findings are the latest wrinkle in an ongoing debate about the use of opioids in medicine in the United States and how to balance the benefits of pain control with the risks associated with this class of drugs, including a growing epidemic of opioid abuse. For nephrologists, finding the right balance is a particularly delicate task.

“We're responsible for optimizing their health-related quality of life, minimizing their symptom burden; and part of that is understanding and treating them if they have substantial pain,” said Sara Davison, MD, MSc, director of the Kidney Supportive Care Research Group at the University of Alberta in Canada. “We, as a community, need to commit to being able to do this in an effective manner, and that also means a safe manner.”

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Opioid abuse in kidney patients presents complex choices for nephrologists; CMS releases opioids roadmap; and ASN advocates for safe alternatives

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studies have established this enzyme as a metabolic regulator and a potentially important target for obesity and type 2 diabetes drugs. Studies in whole-body PTP1B knockout mice have shown improved insulin sensitivity, enhanced glucose tolerance, and resistance to obesity when the mice are fed a high-fat diet, which is associated with increased leptin signaling.

Studies using tissue-specific PTP1B disruption have shown distinct metabolic actions, including reduction in complement-mediated glomerular injury and protection against proteinuria. The new study examined the effects of PTP1B disruption in podocytes, which are believed to be involved in the pathogenesis of diabetic nephropathy.

Previous studies in rodents with podocyte injury have reported glomerular upregulation of PTP1B, particularly in podocytes.

Haj and colleagues generated mice with podocyte-specific PTP1B disruption, then compared the effects on renal function in normoglycemic animals versus those with hyperglycemia, induced either by a high-fat diet or by streptozocin. Both treatments led to increased expression of PTP1B by the kidneys. Disruption of podocyte-specific PTP1B in the presence of normoglycemia, however, did not affect renal function.

After induction of hyperglycemia, podocyte-specific PTP1B knockout mice did not show the signs of renal damage—including albuminuria, renal injury, and elevated serum glucose levels—observed in hyperglycemic control animals.

“Collectively, these findings demonstrate that podocyte PTP1B disruption protects renal function under streptozocin- and high-fat-diet-induced hyperglycemia and identify podocytes as contributors to the beneficial effects of PTP1B deficiency,” the researchers wrote.

The reduction in hyperglycemia-induced renal injury was confirmed in histopathologic studies: animals with podocyte PTP1B disruption had less evidence of damage to podocyte structure and foot processes. Further experiments showed increased renal insulin signaling in podocyte PTP1B-knockout mice, along with decreased inflammation. Reductions in fibrosis, along with other findings, suggested that podocyte PTP1B disruption enhanced autophagy, an important regulator of kidney function and a suggested protective mechanism against podocyte injury.

In vitro studies in E11 “knockdown” mouse podocytes showed enhanced insulin signaling and autophagy in the presence of high glucose levels. These changes were reversed in cells with reconstituted expression of PTP1B. The protective effect of PTP1B deficiency against fibrosis was reduced in E11 cells treated with a pharmacologic knockdown inhibitor.

“Altogether, these data are in keeping with in vivo findings and are consistent with cell-autonomous effects that are due to PTP1B deficiency,” the researchers said.

The findings lend potentially important new insights into the mechanisms of podocyte dysfunction and its contribution to the pathogenesis of diabetic nephropathy. In the presence of hyperglycemia, podocyte PTP1B expression is increased. Experimental disruption or deficiency of podocyte-specific PTP1B reduces hyperglycemia-induced renal injury while preserving glucose control.

“These beneficial effects of podocyte PTP1B disruption are associated with improved insulin signaling and enhanced autophagy, with a likely causal relationship.

“These findings identify PTP1B in podocytes as a contributor to renal function under hyperglycemia,” Haj and his colleagues conclude. They note their results are consistent with previous recent models of podocyte injury, including reports that podocyte PTP1B disruption protects against glomerular and podocyte injury.

The unique contribution of the study is its focus on disruption of PTP1B in podocytes only, rather than the entire organism. In a press release, coauthor José Manuel Villalba of the University of Cordoba commented that PTP1B “is crucial in regulating the glucose metabolism. In certain circumstances, such as hyperglycemia, exclusive inhibition of the protein in podocytes will benefit the entire organism.”

Could PTP1B and its substrates serve as therapeutic targets? Possibly, but as Villalba notes, “There is still a lot of work to be done.” Because PTP1B is present throughout the body and serves a number of important functions, inhibition of this protein could have negative effects. However, if a drug could be developed that selectively inhibited PTP1B mainly in kidney cells, it might provide a new approach to treating or preventing diabetic nephropathy.