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Joslin researchers gain new understanding of diabetes and kidney disease

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Scientists at Joslin Diabetes Center have identified biological mechanisms by which glucagon-like peptide-1 (GLP-1), a gut hormone, protects against kidney disease, and also mechanisms that inhibit its actions in diabetes. The findings, which are reported today online by Diabetes, may lead to the development of new therapeutic agents that harness the actions of GLP-1 to prevent the harmful effects of hyperglycemia on renal endothelial cells.

Renal complications, also known as diabetic nephropathy, are one of the most life-threatening complications of diabetes that often lead over time to end-stage renal disease (ESRD). About a half million people in the US – 44 percent of whom are diabetics -- have ESRD, which requires dialysis or kidney transplantation. As a result, investigating the relationship of diabetes to renal dysfunction is a major focus of diabetes research. "We are very eager to develop new treatments for diabetic kidney disease," says George King, M.D., lead author of the study, and chief scientific officer, head of the Dianne Nunnally Hoppes Laboratory for Diabetes Complications and a professor of medicine at Harvard Medical School.

GLP-1 is an incretin hormone that is produced by the intestine in response to food. GLP-1 increases the secretion of insulin from the pancreas, slows absorption of glucose from the gut, and reduces the action of glucagon – all of which lower glucose levels in the blood. In addition, GLP-1 reduces appetite. The drug, exendin-4 (marketed as Exenatide), which mimics the effects of GLP-1, is used to lower blood

glucose in type 2 diabetes.

Recent studies have reported that GLP-1 improves the function of renal endothelial cells (which regulate blood clotting, immune response and blood vessel activity, among other critical functions, and are impaired by insulin resistance) and can prevent some renal pathologies in diabetic rodents. GLP-1 receptors (GLP-1R), which are abundant in the intestine, are also found in the endothelium and kidney.

The Joslin study investigated the effects of GLP-1 in non-diabetic and diabetic mice with an "overexpression" of the enzyme PKCβ (protein kinase C-beta) which is produced in excess when blood glucose is high. Excess PKCβ can lead to diabetes complications, including kidney disease. PKCβ enhances the action of angiotensin II (Ang II), a peptide hormone that affects renal filtration and blood flow and also regulates blood pressure, which increases inflammation and accelerates the progression of kidney damage.

The study looked at the interactions of GLP-1, PKC-beta and ANG II that affect GLP-1's protective action in renal endothelial cells. "We've been interested in diabetic kidney disease for a long time, particularly the role of PKCβ and Ang II in promoting kidney damage," says Dr. King. "We were interested in investigating how GLP-1 could protect against the effects of hyperglycemia on renal function."

Josin researchers made two major findings: They identified the mechanisms by which GLP-1 can induce protective actions on the glomerular (renal) endothelial cells by inhibiting the signaling pathway of Ang II and its pro-inflammatory effect; and demonstrated a dual signaling mechanism by which hyperglycemia, via PKCβ activation, can increase Ang II action and inhibit GLP-1's protective effects by reducing the expression of GLP-1 receptors in the glomerular endothelial cells. "We know that people with diabetes are more sensitive to Ang II; our

data suggests one reason why," says Dr. King.

The results suggest that effective therapeutic agents could be developed to enhance the effects of GLP-1R on the endothelium which may prevent glomerular endothelial dysfunction and slow the progression of diabetic nephropathy. "We now know that increased PKCβ decreases GLP-1R which makes the kidney less responsive to treatment with GLP-1-based drugs. Possible new treatments could combine PKCβ inhibitors with higher doses of GLP-1 agonists. GLP-1 is one potential pharmaceutical that could both lower glucose and minimize the toxic effects of Ang II to lower the risk of kidney diseases," says Dr. King.

Provided by Joslin Diabetes Center

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