A gut feeling

By Tim Fulmer, Staff Writer

Many treatments for metabolic disorders such as obesity and type 2 diabetes directly target the brain or liver (*see* **Figure 1, "Controlling the liver via the gut"** *and* **Table 1, "Targeting diabetes and obesity"**).[1] Although neural communication was previously known to exist between the small intestine and the brain to curb food intake,[2,3] and between the brain and the liver to mediate regulation of liver glucose production,[4,5] a new study in *Nature* now closes the loop to reveal a complete "intestine-brain-liver" neural circuit.

Tony Lam and colleagues propose that disconnects in this circuit could be responsible for the aberrant glucose homeostasis that underlies insulin resistance, obesity and type 2 diabetes. Thus, the authors suggest that targeting nodes within the circuit could restore insulin sensitivity in people with obesity and type 2 diabetes without directly interfering with liver and brain physiology.[6]

Lam, corresponding author on the paper, is a researcher in the Division of Cellular and Molecular Biology at the **Toronto General Hospital Research Institute** and an assistant professor of physiology and medicine at the **University of Toronto**.

The team's study in rats shows that a lipid-sensing mechanism in the upper intestine acts through the brain to downregulate liver glucose production in the presence of nutrient excess. Infusing small quantities of lipids directly into the upper portion of the small intestine significantly decreased liver glucose production compared with that in rats that received vehicle control ($p<0.001$).

Surgically or pharmacologically blocking neurotransmission pathways between the intestine and the brain or between the brain and the liver abolishes the ability of infused lipids to alter liver glucose production. Therefore, upper intestinal lipids require a gut-brain-liver circuit to mediate their effects on the liver.

"Our research shows for the first time how lipid-sensing regions of the intestine can act remotely through the brain to influence liver glucose homeostasis," Lam told *SciBX*. "Thus, compounds that activate this mechanism could potentially reduce liver glucose production and normalize blood glucose levels in metabolic disorders."

The observation that lipids in the upper small intestine "can produce profound and rapid decreases in hepatic glucose output" prior to absorption into the blood "will attract a lot of interest in both the obesity and type 2 diabetes research communities," Jeffrey Johnson, principal scientist of biological sciences at **Metabolex Inc.**, told *SciBX*.

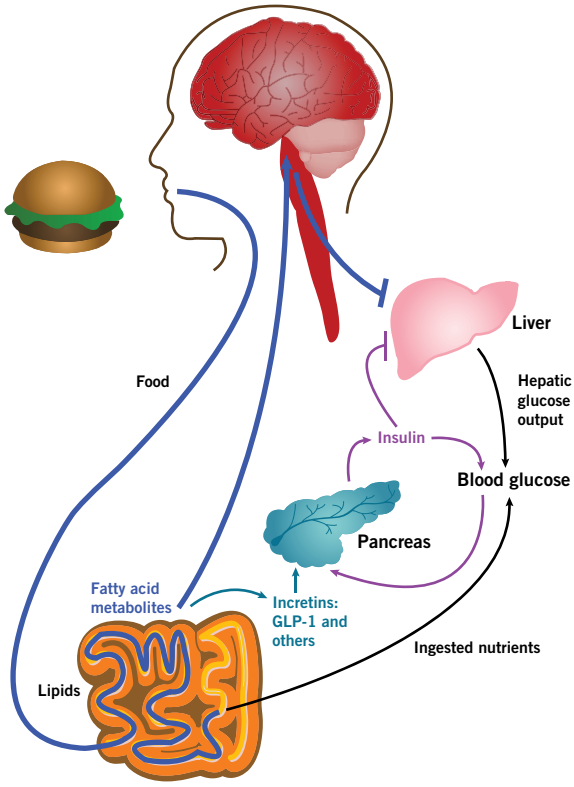

Figure 1. Controlling the liver via the gut. The variety of tissues implicated in metabolic disorders has generated a broad range of therapeutic strategies that generally can be divided into those that target the CNS and those that target peripheral organs such as the liver and pancreas (*see* **Table 1, "Targeting diabetes and obesity"**). But a study in *Nature*[6] suggests that restoration of plasma glucose levels could begin in cells that line the lumen of the small intestine. There, lipids derived from ingested nutrients are metabolized to fatty acids that trigger an intestine-brain-liver neural circuit, which ultimately reduces liver glucose output (blue pathway). A therapeutic targeting the lipid-sensing cells thus could help treat diabetes and obesity prior to entering systemic circulation.

Another metabolic pathway originating from the intestines implicates the release of incretins into the bloodstream. Companies already have therapeutics that target this process. For example, Byetta exenatide, a glucagon-like peptide-1 (GLP-1) receptor agonist marketed by **Amylin Pharmaceuticals Inc.** (NASDAQ:AMLN) and **Eli Lilly and Co.** (NYSE:LLY), mimics the action of incretin GLP-1 by increasing pancreatic secretion of insulin—which subsequently reduces liver glucose output and restores healthy plasma glucose levels.

Metabolex's MBX-102, a partial peroxisome proliferation–activated receptor-γ (PPAR-γ) agonist, is in Phase II/III testing to treat type 2 diabetes.

Although giving small quantities of lipids may not be a practical approach in humans because this mechanism may be impaired in patients who are obese and/or diabetic, Johnson noted that it would be worth finding other ways to activate such lipid-sensing cells in the small intestine "in order to selectively suppress the unregulated hepatic glucose output that characterizes type 2 diabetes."

Cell-surface receptors and ion channels on the lipid-sensing cells would be obvious initial targets for small molecule modulation of the gut-brain-liver pathway, he said. "Lipid metabolism pathways within those cell types, or in the intestinal mucosa itself, could also be targeted."

Table 1. Targeting diabetes and obesity. A number of diabetes and obesity compounds in late-stage development and on the market target various pathways in different organs. Some of the most advanced programs against a given target are listed below. Compounds may affect additional tissue types than those noted.

Company	Product	Product description	Indication	Status
Adipose tissue, muscle & liver				
GlaxoSmithKline plc (LSE:GSK; NYSE:GSK)	Avandia rosiglitazone	Peroxisome proliferation–activated receptor-γ (PPAR-γ) agonist	Diabetes	Marketed
Takeda Pharmaceutical Co. Ltd. (Tokyo:4502)/Eli Lilly and Co. (NYSE:LLY)	Actos pioglitazone	PPAR-γ agonist	Diabetes	Marketed
Novo Nordisk A/S (CSE:NVO; NYSE:NVO)	Levemir	Insulin receptor agonist	Diabetes	Marketed
Novo Nordisk	Novolog	Insulin receptor agonist	Diabetes	Marketed
Brain/CNS				
sanofi-aventis Group (Euronext:SAN; NYSE:SNY)	Acomplia/Zimulti rimonabant	Cannabinoid CB1 receptor antagonist	Obesity	Marketed
Abbott Laboratories (NYSE:ABT)	Meridia sibutramine	Serotonin, norepinephrine and dopamine reuptake inhibitor	Obesity	Marketed
Amylin Pharmaceuticals Inc. (NASDAQ:AMLN)	Symlin pramlintide	Amylin receptor agonist	Diabetes; obesity	Marketed (diabetes); Phase II (obesity)
VeroScience LLC/S2 Therapeutics Inc.	Cycloset bromocriptine	Dopamine D2 receptor agonist	Diabetes	Phase III complete
Orexigen Therapeutics Inc. (NASDAQ:OREX)	Contrave naltrexone/ buproprion	Opioid receptor antagonist and norepinephrine and dopamine reuptake inhibitor	Obesity	Phase III
Merck & Co. Inc. (NYSE:MRK)	Taranabant	Cannabinoid CB1 receptor agonist	Obesity	Phase III
7TM Pharma A/S	Obinepitide	Neuropeptide Y (NPY) receptor agonist	Obesity	Phase II
Nastech Pharmaceutical Co. Inc. (NASDAQ:NSTK)	PYY-3-36	NPY receptor agonist	Obesity	Phase II
Circulation/Vasculature				
Merck	Januvia sitagliptin	Dipeptidyl peptidase-4 (DPP-4) inhibitor	Diabetes	Marketed
Novartis AG (SWX:NOVN; NYSE:NVS)	Galvus vildagliptin	DPP-4 inhibitor	Diabetes	Marketed
Intestines				
Roche (SWX:ROG)	Alli/Xenical orlistat	Pancreatic lipase inhibitor	Obesity	Marketed
Kidney				
AstraZeneca plc (LSE:AZN; NYSE:AZN)/ Bristol-Myers Squibb Co. (NYSE:BMY)	Dapagliflozin	Sodium-glucose cotransporter 2 (SGLT2) inhibitor	Diabetes	Phase III
Liver				
Metabasis Therapeutics Inc. (NASDAQ: MBRX)	MB07803	Fructose 1,6-bisphosphatase inhibitor	Diabetes	Phase II
Pancreas				
Amylin/Eli Lilly	Byetta exenatide	Glucagon-like peptide-1 (GLP-1) receptor agonist	Diabetes	Marketed
Novartis	Starlix nateglinide	ATP-dependent potassium channel (KATP) blocker	Diabetes	Marketed
Novo Nordisk	Prandin repaglinide	KATP blocker	Diabetes	Marketed
sanofi-aventis	Amaryl glimepiride	KATP blocker	Diabetes	Marketed

Identification of the intestinal hormones that mediate signaling of the sensor cells to the brain could also result in new targets for therapeutic intervention, said Nancy Thornberry, VP and research head of the diabetes division of **Merck & Co. Inc.**

It is not yet known which hormones fulfill that function, and Lam agreed that "investigating the potential role of gut hormones in signal transmission between the intestine and nervous system is an important next step."

He noted the gastrointestinal peptide cholecystokinin (CKK) is one example of such a hormone. Upper intestinal lipid infusions were previously shown by another lab to induce local release of CKK.[7]

More broadly, the *Nature* paper points out "the importance of investigating the role of nonendocrine pathways in metabolic control and dysfunction," said Silvana Obici, associate professor of psychiatry and endocrinology in the Obesity Research Center at the **University of Cincinnati**.

"Lam's research suggests that upon sensing nutrients like lipids, some intestinal cells may release factors that directly stimulate local nerve endings rather than enter into systemic circulation in an endocrine fashion," she told *SciBX*. "This finding could open up a broad new area of metabolic research into molecules that transmit gut signals directly to the brain via the vagus cranial nerve."

Although further elucidation of the gut-brain-liver axis may turn up a wealth of potential targets, the *Nature* paper also revealed that the upper intestinal lipid-sensing mechanism may be easily impaired by a fat-heavy diet. Those findings provide yet another link between obesity and diabetes.

In rats, three days of a high-fat diet were sufficient to abolish reductions in liver glucose production caused by intestinal lipids compared with what was seen in animals fed a regular diet. This finding prompted the authors to state that "in the early onset of diet-induced insulin resistance, the intestine may have acquired defect(s) in lipid sensing, hindering glucose homeostasis regulation."

Obici agreed. "In susceptible individuals, it may be that these sensors are the first line of defense to go. As a consequence, one would predict at least partial loss of control over liver glucose production, insulin resistance and increased circulating levels of insulin and glucose—the precursors of type 2 diabetes," she said.

Indeed, said Johnson, "high-fat diets have been shown to have profoundly negative impacts on glucose metabolism, and the work described in the *Nature* paper could explain a component of this metabolic dysregulation."

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