Adipsin meets β cells

By Tracey Baas, Senior Editor

The long-standing mystery of how adipsin regulates metabolism has been solved by a Harvard-led team that has shown the enzyme can increase insulin secretion by generating the peptide complement 3a.¹ Its therapeutic potential may hinge on showing that the effect persists with chronic dosing and does not trigger inflammation or other unwanted side effects.

The team is now planning to test recombinant adipsin in long-term safety and efficacy studies in mouse models of diabetes.

The study was led by Bruce Spiegelman, whose research group identified adipsin as one of the first adipokines—adipose tissue-secreted cytokines—in 1987.² Adipsin was subsequently shown to have the same enzymatic activity as a previously discovered protein called complement factor D (CFD). CFD and adipsin were later shown to be

the same protein, a rate-limiting enzyme in the alternative complement activation pathway.^{3–5}

Spiegelman is a professor of cell biology and medicine at **Harvard Medical School** and cofounder and chair of the scientific advisory board at diabetes and obesity company **Ember Therapeutics Inc.** The company, which focuses on brown fat biology, has not licensed the adipsin findings.

Adipsin cleaves complement factor B (CFB) in the alternative complement pathway, thus catalyzing the formation of C3 convertase and leading to a hydrolysis cascade that produces various complement fragments including complement 3a (C3a), C3b, C5a and C5b.³

Previous studies had shown that adipsin levels and activity were lower in animal models of obesity and diabetes than in lean controls, which suggested that the protein might regulate energy homeostasis and metabolism.^{2,6} But the relevance for metabolism remained unknown. Thus, Spiegelman's team set out to uncover how adipsin might be affecting insulin secretion or glucose homeostasis.

In mice fed a high-fat diet for 16 weeks, *adipsin* knockout mice showed significantly decreased glucose tolerance compared with wild-type mice ($p < 0.01$), but both knockouts and wild-type mice responded similarly to insulin. That suggested the changes were not due to insulin resistance. The high-fat diet-fed *adipsin* knockout mice showed diminished insulin secretion in response to glucose but had no significant differences in islet morphology or β cell distribution.

Next, the team tested whether raising adipsin levels could improve symptoms in a mouse model of established diabetes based on *leptin* deficiency. These models also exhibit lower levels of adipsin. Adenovirus-mediated adipsin overexpression in the liver for five days improved glucose homeostasis and increased insulin secretion compared with expression of a control protein.

Because adipsin is not produced within the islets of Langerhans—where β cells reside—the researchers hypothesized that adipsin could be acting remotely to produce a complement component that would circulate and act on β cells.

Figure 1. Controlling insulin secretion via the adipose tissue–islet connection. 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). New work from Lo *et al.* suggests that an adipose tissue–islet connection may also help regulate liver glucose output (red pathway).

The authors propose that adipsin (complement factor D; CFD) secreted from adipose tissue produces complement 3a (C3a) that acts remotely at the islets of Langerhans, where β cells reside, to stimulate insulin secretion and ultimately reduce liver glucose output. Whether adipsin would compete with glucagon-like peptide-1 (GLP-1) analogs or work in combination to produce additive effects on insulin secretion remains to be seen.

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Australian National University
Medical School

Using flow cytometry, the team showed that the only complement cascade receptor expressed by the islets was complement component 3a receptor 1 (C3AR1; C3AR). The group thus hypothesized that C3a might be the factor regulating glucose homeostasis.

Two lines of evidence supported that hypothesis. First, a C3AR1 antagonist blocked improvements in glucose tolerance and insulin secretion in diabetic mice overexpressing adipsin in the liver. Second, C3a produced a 30%–40% increase in insulin secretion compared with adipsin, C5a or C3 in an *in vitro*, glucose-stimulated insulin secretion assay in mouse islets. Similar results were found in islets from diabetic and normal mice.

Thus, Spiegelman's team proposed a mechanism in which adipsin cleaves C3 to produce C3a, which interacts with C3AR1 to act on β cells (see Figure 1, "Controlling insulin secretion via the adipose tissue–islet connection").

Finally, the team sought to determine whether adipsin levels were dysregulated in patients with type 2 diabetes with β cell failure, defined as patients who were receiving insulin therapy. Patients with β cell failure showed significantly lower levels of serum adipsin and adipsin mRNA in adipose tissue than patients without β cell failure ($p < 0.05$).

Results were published in *Cell*. The study also included researchers from the **Karolinska Institute, University of Ancona** and **University of Leipzig**.

Complementary experiments

The new connection between adipose tissue and islet function provides a valuable mechanistic link, but the therapeutic potential of adipsin in obesity and diabetes still requires longer-term proof of concept.

Christopher Nolan told *SciBX*, "The findings are particularly interesting as signaling via adipsin may be an important mechanism by which there is cross-talk between adipose tissue and the islet."

Nolan is a professor of endocrinology at the **Australian National University Medical School** and director of ACT Diabetes Services at **Canberra Hospital**.

However, Takashi Kadowaki, chairman of the Department of Diabetes and Metabolic Diseases at **The University of Tokyo**, cautioned that the evidence for adipsin as a therapeutic would require longer-term studies because the study only involved five-day, adenovirus-mediated overexpression.

"While the paper suggests that systemic replenishment of adipsin improves hyperglycemia in diabetic mice by boosting insulin secretion, this was only shown to be true with short-term administration," he said. "The effect of adipsin needs yet to be evaluated over the long term for its ability to maintain β cell function over time in the type 2 diabetic mouse model."

Nolan agreed that longer-term studies are needed, in particular because the study showed that adipsin and C3a increased islet oxygen consumption via ATP-coupled respiration.

"It will be important to show that an effect to increase insulin secretion can be sustained in the long term. A mechanism of action that augments insulin secretion but at the cost of increased β cell injury through increased oxidative stress would be counterproductive," he said.

He added that the potential for unwanted inflammation caused by adipsin or C3a was a concern. "The adipsin-deficient mice had markedly reduced levels of adipose tissue inflammation, indicating that adipsin may have proinflammatory effects in adipose tissue, and perhaps elsewhere, that may not be wanted when using it to treat diabetes," said Nolan. "Inflammation should be further characterized."

Spiegelman noted that the team will look for obvious signs of inflammation and other toxicities in future studies of diabetic mouse models treated with adipsin or C3a.

Jacob Petersen, a professor and corporate VP in the diabetes research unit at **Novo Nordisk A/S**, thought that before future therapeutic potential could be realized, it would be necessary to generate stable adipsin or C3a analogs with more favorable pharmacokinetic and pharmacodynamic properties than the parent compounds.

Indeed, Spiegelman's team plans to study the antidiabetic effects of recombinant adipsin in mouse models of diabetes. He has proposed that the approach could be safer than using C3a itself because adipsin might generate C3a in the vicinity of β cells by docking with other complement components. C3a can cause anaphylaxis.

Spiegelman declined to give details about his team's recombinant protein strategy.

"If the team's idea about the islet being a 'docking station' is true, and C3a is—at least to some degree—formed locally at the islets, then adipsin therapy would be a safer strategy than using modified C3a, avoiding unwanted systemic inflammation," said Petersen.

Carey Lumeng, an associate professor of pediatrics and physiology at the **University of Michigan Medical School**, cautioned that it remains unclear where C3a is being produced by adipsin. "It has yet to be shown that adipsin works at the islet to activate C3a production. It's possible that the activation is occurring somewhere else," he said.

Lumeng and Nolan both said that it is also too early to rule out whether adipsin is acting through other mechanisms. "The adenovirus-mediated overexpression of adipsin resulted in major reductions in hepatic gluconeogenic enzymes, suggesting the possibility that the improved glucose tolerance could have been a consequence of a more direct effect on the liver rather than via its effects on the islet," Nolan said. "This possibility should be explored."

Petersen said that adipsin could compete with marketed therapies that induce insulin secretion, such as glucagon-like peptide-1 (GLP-1) analogs and dipeptidyl peptidase-4 (DPP-4; CD26) inhibitors, which also help improve β cell function.

Although there is not yet evidence that adipsin could provide an advantage over these drugs, alternative approaches to maintain and restore β cell function are still needed as most patients on these drugs ultimately progress to insulin therapy.

Indeed, Petersen said that he would be interested in seeing combination studies testing adipsin with GLP-1 analogs. "An interesting path forward could be to test adipsin or C3a in combination with GLP-1," he said. "If the effect is additive and the side-effect profile reasonable, then this could represent an interesting new class of drugs. If not, it is

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GLP-1 agonists include Novo’s Victoza liraglutide, which is marketed to treat diabetes and in registration to treat obesity.

Lumeng added that he would like to see the effect of marketed antidiabetic treatments on adiponectin activity and adiponectin secretion from adipose tissue. “It’s possible that other antidiabetic treatments have the ability to increase adiponectin activity or production as part of their effect,” he said.

He also noted that one therapy targeting adiponectin, **Roche’s Genentech Inc.** unit’s mAb Fab lampalizumab, is in clinical trials to treat macular degeneration and is being delivered by intravitreal injection. “Based on Spiegelman’s study and the possibility that adiponectin works as an endocrine molecule, there may be a need to monitor insulin and glucose levels in these patients and examine if there is an effect on any patients that are also diabetic or prediabetic subjects.”

A patent application has been filed on adiponectin as a diagnostic marker and as a possible therapeutic to treat diabetes. Licensing is available through the office of technology transfer at the **Dana-Farber Cancer Institute**.

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