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Blocking p75 NTR in diabetes

By Lauren Martz, Staff Writer

University of California, San Francisco researchers have shown that genetic deletion of the p75 neurotrophin receptor improves insulin sensitivity in diabetic mice.[1] Although targeting this receptor may offer a new way to treat insulin resistance, the challenge will be figuring out how to inhibit it in skeletal muscle and adipose tissue without impairing its function in neurons.

Insulin resistance in muscle and fat cells reduces glucose uptake, leading to chronically high blood glucose and type 2 diabetes. In most forms of insulin resistance, trafficking of solute carrier family 2 facilitated glucose transporter member 4 (SLC2A4; GLUT4) to the plasma membrane is impaired.[2] Unfortunately, it has remained unclear how to target GLUT4 to improve glucose uptake and insulin sensitivity.

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Prior work by groups at the **University of Liverpool** and **E. Medea Scientific Institute** had shown that the p75 neurotrophin receptor (p75 NTR), a protein originally identified in the nervous system, is expressed in white adipose tissue and skeletal muscle tissue, in which it interacts with small GTPases that regulate GLUT4 trafficking.[3,4] In the nervous system, p75 NTR is involved in many neuronal functions including the development of sensory neurons.[5]

Based on those findings, Katerina Akassoglou and colleagues at UCSF hypothesized that targeting p75 NTR might indirectly influence GLUT4 trafficking in muscle and fat tissues and thus improve glucose uptake and insulin sensitivity.

Akassoglou is associate investigator of neurology at UCSF's **Gladstone Institute of Neurological Disease**. The team also included researchers from the **University of California, San Diego**, the **University of Michigan** and **Baylor College of Medicine**.

The group first showed that knockout of *p75 ntr* in mice fed a normal diet did not alter food consumption or body weight but lowered glycemic excursions during a glucose tolerance test and increased hypoglycemia by 30%. Those results suggested insulin sensitivity in the knockouts was greater than that in wild-type controls. Also in the knockout mice, insulin-stimulated glucose disposal was higher than that in wild-type controls.

Insulin-stimulated glucose uptake was greater in adipocytes derived from the *p75 ntr*$^{-/-}$ mice than in cells from wild-type mice. The same effect was seen from small hairpin RNA–mediated *p75 ntr* knockdown and in myocytes. Those findings suggested that blocking p75 NTR signaling in skeletal muscle and white adipose tissue could help increase insulin sensitivity and glucose tolerance.

Also in adipocytes, coimmunoprecipitation studies showed p75 NTR forms a complex with the RAB5 family members RAB5A member RAS oncogene family (RAB5A) and RAB31 member RAS oncogene family (RAB31). In *p75 ntr*$^{-/-}$ adipocytes, expression of a dominant negative Rab5a mutant prevented the increase in glucose uptake caused by *p75 ntr* knockout, suggesting p75 NTR interacts with RAB5 GTPases to block GLUT4 trafficking and glucose uptake.

The findings were published in the *Proceedings of the National Academy of Sciences*.

Akassoglou told *SciBX* that next steps include identifying inhibitors that specifically block the interaction of RAB5 family GTPases with p75 NTR.

"Potentially, the work in this paper could lead to the development of agents that can correct a key defect in human type 2 diabetes, which is reduced glucose uptake in white adipose tissue and skeletal muscle," said Cord Dohrmann, CSO of **Evotec AG**. "Based on the phenotype of p75 NTR mice, this may be possible without causing weight gain, which is a major liability of the currently marketed TZD class of insulin-sensitizing drugs."

Current strategies to improve insulin sensitivity include agonizing peroxisome proliferation–activated receptor-γ (PPARG; PPARγ) with compounds including the thiazolidinedione (TZD) class of agonists.

However, PPARG agonists "lack specificity and cause elevation in lipid levels. These drugs are also associated with fluid retention, weight gain and increases in the number and size of adipocytes. There are also a variety of other side effects including increased risk for congestive heart failure," said Richard Gregg, CSO of **Vitae Pharmaceuticals Inc.**

Vitae has a hydroxysteroid 11β dehydrogenase 1 (HSD11B1; HSD1) inhibitor in Phase I testing to treat type 2 diabetes. The compound is partnered with **Boehringer Ingelheim GmbH**.

Evotec and **Harvard University** "have conducted screens to identify novel mechanisms and targets that enhance β cell mass and function. These screens have identified several high-potential target candidates, a number of which have reached initial proof of concept in animal models," Dohrmann told *SciBX*.

Evotec's β cell regeneration factor, EVT 770, is in preclinical testing to treat diabetes. The compound is partnered with **AstraZeneca plc**.

Selective targeting and side effects

The big challenge moving forward will be to figure out how to target p75 NTR in muscle and adipose tissue without blocking the protein's function in neural tissue.

"p75 is a difficult target because it has a lot of biological implications. In addition to the small GTP-binding proteins involved in glucose

transporter activity, it also interacts with other small binding molecules and has a lot of functions in neuronal activity," said Gregg. "Whether a new therapeutic would be able to have specificity for the beneficial effects on insulin sensitivity without the CNS toxicity is a concern."

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Barbara Hempstead, professor of medicine at **Weill Cornell Medical College**, agreed. "p75-null animals have altered glucose homeostasis but also have other consequences including defects in sensory perception, shortened lifespan and hippocampal defects. Therefore, it might be helpful to confirm the results in a targeted manner," she said.

Dohrmann added, "In light of the fact that p75 knockout mice have a range of neuronal defects, any interference with the receptor probably needs to be highly specific."

"Selective targeting of the interaction of p75 NTR with RAB5A in peripheral tissues might lead to therapies with less side effects," said Akassoglou. However, she said, "appropriate methodologies applicable for targeting p75 NTR will have to be developed and tested."

Another issue related to blocking p75 NTR, according to Gregg, is that "p75 NTR appears to be part of an intracellular protein-protein interaction. You need intracellular activity from a therapeutic like a small molecule, yet it is difficult to target protein-protein interactions with small molecules. Protein biologics are better suited for these kinds of interactions, but they are hard to get into cells."

He added that an important next step would be to gain a better understanding of the structure-function interaction at the crystallography level. "If the team is able to identify a site for small molecule binding with therapeutic activity, it still could be feasible to target the interaction, although still very hard," he said.

In addition to targeting p75 NTR interactions that are specific for insulin signaling, specificity and reduced side effects could be achieved by selectively targeting the appropriate tissues.

"Another next step would be to look at the effects of interfering with RAB5A and RAB31 interactions in various cell types. Specific targeting to adipocytes and myocytes in the periphery could give you the efficacy in diabetes without the dysfunction in neurons. Again, though, this would be difficult to execute," said Gregg.

Akassoglou told *SciBX* that UCSF has filed a patent application covering the findings and that the IP is available for licensing.

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COMPANIES AND INSTITUTIONS MENTIONED

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