Getting AGRP on obesity

By Kai-Jye Lou, Staff Writer

Researchers in New York have identified G protein-coupled receptor 17 as a target on agouti related protein-expressing neurons, which are known to regulate multiple factors related to obesity.¹ The findings open up a new molecular signaling pathway to mine for targets to control obesity—earlier attempts to inhibit these neurons via insulin and leptin signaling pathways have had little success.

Inhibition of hypothalamic neurons that express agouti related protein (AGRP) is known to decrease food intake, promote body leanness and improve glucose homeostasis. Although insulin and leptin inhibit the activity of these neurons via their respective receptors, studies to evaluate the activation of these hormonal signaling pathways have suggested that neither pathway alone exerts

full control over AGRP neuron-mediated food intake and glucose homeostasis.^{2,3}

Moreover, resistance to insulin and leptin develops in response to diet-induced obesity.⁴

Thus, a group led by Domenico Accili, professor of medicine and director of the **Columbia University** Diabetes and Endocrinology Research Center, looked into alternative pathways that could be targeted to inhibit the activity of AGRP neurons.

The group first looked upstream at the forkhead box O1 (FOXO1) transcription factor because it regulates both leptin and insulin signaling (see Figure 1, “Model for processes mediated by FOXO1 in AGRP neurons”).^{5,6} In mice, knockout of *Foxo1* in hypothalamic *Agrp* neurons decreased food intake and body fat mass and increased body lean mass, glucose homeostasis and sensitivity to both leptin and insulin compared with wild-type *Foxo1* expression.

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Columbia University

Figure 1. Model for processes mediated by FOXO1 in AGRP neurons. Researchers have now elucidated the role of forkhead box O1 (FOXO1) transcription factor signaling in hypothalamic neurons that express agouti related protein (AGRP). In the process, the researchers identified G protein-coupled receptor 17 (GPR17) as a potential therapeutic target to help control obesity.

(I) In AGRP neurons with functional FOXO1, activation of GPR17 increases food intake [a]. This is thought to occur via modulation of downstream ion channels [b] in a manner that stimulates the release of neuropeptide Y (NPY) and AGRP [c]. The peptide and protein are both known to increase food intake.

Antagonizing GPR17 has the opposite effects.

(II) Knocking out *FOXO1* in AGRP neurons decreases the expression of GPR17 [a] and leads to less food intake than normal *FOXO1* expression. Loss of the transcription factor also improves glucose homeostasis, increases sensitivity to insulin and leptin [b] and leads to greater lean body mass.

At this time, it is not known whether GPR17 antagonism itself will increase glucose homeostasis, body leanness and sensitivity to leptin and insulin. (Figure based on Figure 7G in ref. 1.)

However, FOXO1 is a transcription factor and not readily druggable. Thus, Accili's team used transcriptional profiling to identify downstream targets of Foxo1 in the mouse Agrp neurons.

"After observing the beneficial effects in the *Foxo1*-deficient mice, we wanted to know whether there is a *FOXO1*-regulated pathway that would allow us to skirt around direct targeting of the insulin and leptin receptors" and the transcription factor, said Accili.

Transcriptional profiling studies revealed that *Foxo1*-deficient mouse Agrp neurons had about 10-fold lower *G protein-coupled receptor 17 (GPR17)* mRNA levels than nondeficient Agrp neurons.

In wild-type mice, intraventricular injection of the GPR17 antagonist cangrelor significantly decreased food intake compared with saline injection, whereas an agonist of the receptor increased food intake. These differences were not seen in mice with *Foxo1* knocked out in Agrp neurons.

Cangrelor is a reversible antagonist of purinergic receptor P2Y G protein-coupled 12 (P2RY12; P2Y12). GPR17 has been described as a P2Y-like receptor.⁷

The Medicines Co. and **AstraZeneca plc** have cangrelor in Phase III testing to prevent platelet activation and aggregation in patients undergoing percutaneous coronary intervention.

Results were published in *Cell*. The team included researchers from the **Albert Einstein College of Medicine of Yeshiva University** and **Yale School of Medicine**.

"We got interested in GPR17 for two reasons: we saw a 10-fold reduction in *Gpr17* mRNA expression levels in response to knocking out *Foxo1*, and we also knew of chemical compounds that activate and inhibit the receptor," said Accili.

"The development of resistance has been a key problem with earlier strategies to target AGRP neurons, so G protein-coupled receptors such as GPR17 might provide an alternative route to modulating the endogenous activity of these neurons," added Jens Brüning, director of the **Max Planck Institute for Neurological Research**.

However, he said it will be important to determine whether AGRP neurons could develop resistance against GPR17-targeting strategies.

Accili acknowledged that desensitization effects can occur with molecules that target GPCRs. However, he said a GPR17 antagonist "would not be something that one would use in the chronic setting, and the effect we are most interested in is its ability to reduce food intake, which will be relevant at the time of a meal."

Although loss of efficacy from desensitization effects is a concern, it is generally more relevant to the development of long-acting drugs or those that will be used in chronic settings. Most appetite suppressants that promote weight loss are approved for short-term use of up to 12 weeks, though doctors can prescribe the drugs off-label for longer treatment periods.

A new opportunity

Researchers now want to see a more comprehensive suite of studies characterizing the effects of antagonizing GPR17.

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FOXO1 signaling in these neurons, then worked their way back to GPR17 and showed the effects of modulating the receptor on food intake," said Randy Seeley, a professor and director of the Cincinnati Diabetes and Obesity Center at the **University of Cincinnati**. "The findings show that understanding this circuit could lead to the identification of new targets and strategies for controlling body weight and also clearly demonstrate the mechanistic role that GPR17 plays in this circuit."

Brüning noted that in addition to reducing food intake, antagonizing GPR17 on AGRP neurons also could have beneficial effects on glucose

metabolism. "Based on our own work and that of others, we have demonstrated that these neurons becoming insulin resistant contributes to the deterioration of peripheral glucose metabolism. Thus, altering their activity via GPR17-dependent signaling could circumvent this deterioration," he told *SciBX*.

Moreover, Accili said inhibition of GPR17 has been linked to beneficial cardiovascular effects such as reduced blood clotting, improved perfusion of blood into the heart and improved recovery from stroke.

Accili said his group now is trying to develop and characterize the phenotype of a *Gpr17* knockout mouse.

The team has not yet been able to test the effects of GPR17 antagonism on body leanness, glucose homeostasis and sensitivity to leptin and insulin because cangrelor's short half-life makes it difficult to design such experiments.

Nevertheless, he said his group plans to carry out studies to evaluate the effects of GPR17 antagonism on these FOXO1-regulated processes in AGRP neurons.

His group also is planning to rerun the mouse GPR17 antagonism studies in large animal models such as nonhuman primates.

Columbia has a pending patent covering GPR17-based approaches to treat obesity and diabetes. The work is available for licensing from **Columbia Technology Ventures**, the university's technology transfer arm.

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