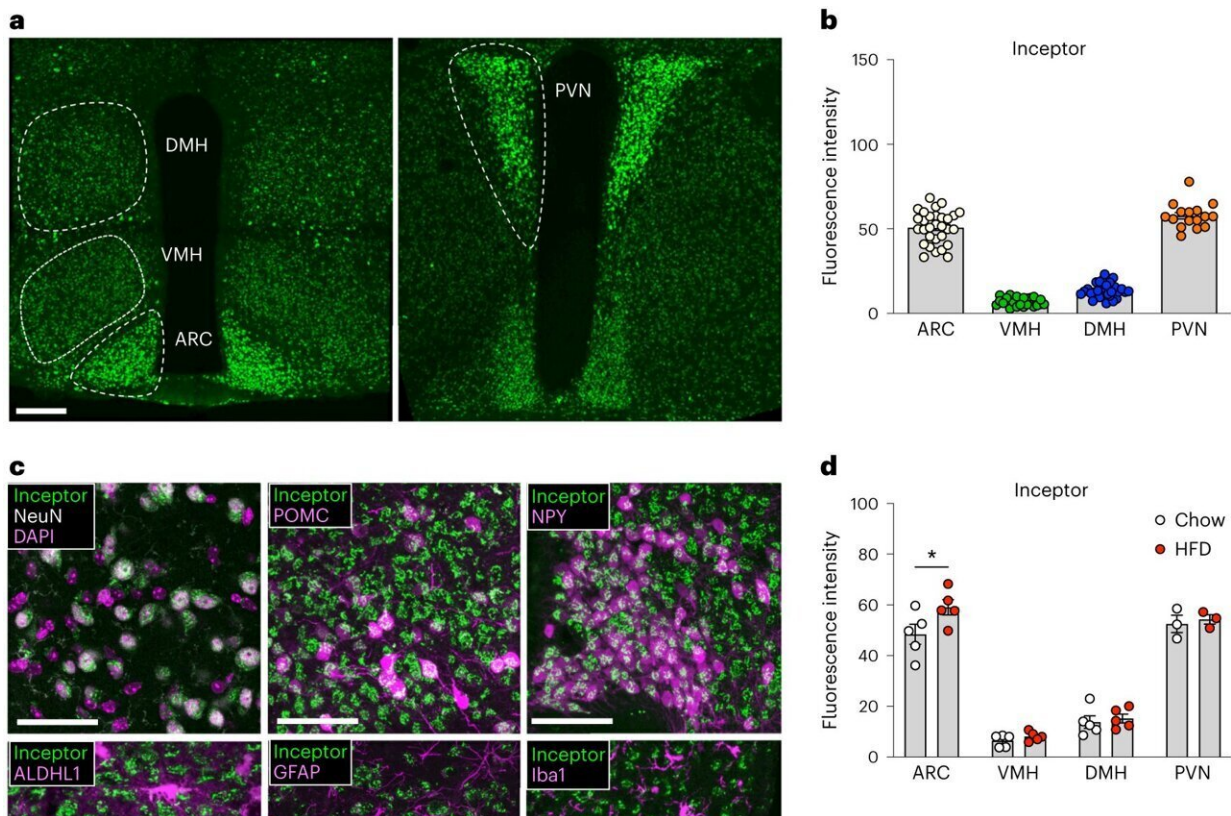


Insulin-inhibitory receptor research offers hope for type 2 diabetes therapy

February 28 2024, by Verena Schulz



Central inceptor immunoreactivity is restricted to neurons, including those regulating energy and glucose metabolism. Credit: *Nature Metabolism* (2024). DOI: 10.1038/s42255-024-00991-3

Research targeting the insulin-inhibitory receptor, or inceptor, unveils promising avenues for beta cell protection, offering hope for causal

diabetes therapy.

A novel study in mice with diet-induced obesity demonstrates that the knock-out of inceptor enhances [glucose regulation](#), prompting its further exploration as a [drug target](#) for type 2 [diabetes](#) treatment.

[These findings](#), led by Helmholtz Munich in collaboration with the German Center for Diabetes Research, the Technical University of Munich, and the Ludwig-Maximilians-University Munich, drive advancements in diabetes research. They have been published in *Nature Metabolism*.

Targeting inceptor to combat insulin resistance in beta cells

Insulin resistance, often linked to abdominal obesity, presents a significant health care dilemma in our era. More importantly, the [insulin resistance](#) of beta cells contributes to their dysfunction and the transition from obesity to overt type 2 diabetes.

Currently, all pharmacotherapies, including insulin supplementation, focus on managing high blood sugar levels rather than addressing the underlying cause of diabetes: beta cell failure or loss. Therefore, research into beta cell protection and regeneration is crucial and holds promising prospects for addressing the root cause of diabetes, offering potential avenues for causal treatment.

With the recent discovery of inceptor, the research group of beta cell expert Prof. Heiko Lickert has uncovered an interesting molecular target. Upregulated in diabetes, the insulin-inhibitory receptor inceptor may contribute to insulin resistance by acting as a negative regulator of this signaling pathway. Conversely, inhibiting the function of inceptor

could enhance insulin signaling—which in turn is required for overall beta cell function, survival, and compensation upon stress.

In collaboration with Prof. Timo Müller, an expert in molecular pharmacology in obesity and diabetes, the researchers explored the effects of inceptor knock-out in diet-induced obese mice. Their study aimed to determine whether inhibiting inceptor function could also enhance glucose tolerance in diet-induced obesity and insulin resistance, both critical pre-clinical stages in the progression toward diabetes.

Removing inceptor improves blood sugar levels in obese mice

The researchers delved into the effects of removing inceptor from all body cells in diet-induced obese mice. Interestingly, they found that mice lacking inceptor exhibited improved glucose regulation without experiencing [weight loss](#), which was linked to increased insulin secretion in response to glucose.

Next, they investigated the distribution of inceptor in the central nervous system and discovered its widespread presence in neurons. Deleting inceptor from neuronal cells also improved glucose regulation in obese mice. Ultimately, the researchers selectively removed inceptor from the mice's beta cells, resulting in enhanced glucose control and a slight increase in beta cell mass.

Research for inceptor-blocking drugs

"Our findings support the idea that enhancing insulin sensitivity through targeting inceptor shows promise as a pharmacological intervention, especially concerning the health and function of beta cells," says Timo Müller.

Unlike intensive early-onset insulin treatments, utilizing inceptor to enhance beta cell function offers promise in alleviating the detrimental effects on blood sugar and metabolism induced by diet-induced obesity. This approach avoids the associated risks of hypoglycemia-associated unawareness and unwanted weight gain typically observed with intensive insulin therapy.

"Since inceptor is expressed on the surface of pancreatic beta cells, it becomes an accessible drug target. Currently, our laboratory is actively researching the potential of several inceptor-blocking drug classes to enhance beta cell health in pre-diabetic and diabetic mice. Looking forward, inceptor emerges as a novel and intriguing molecular target for enhancing beta cell health, not only in prediabetic obese individuals but also in patients diagnosed with type 2 diabetes," explains Heiko Lickert.

More information: Grandl, G. et al, Global, neuronal or β cell-specific deletion of inceptor improves glucose homeostasis in male mice with diet-induced obesity. *Nature Metabolism* (2024). [DOI: 10.1038/s42255-024-00991-3](https://doi.org/10.1038/s42255-024-00991-3)

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