

An Orally Active Small Molecule Mimicking Insulin with Anti-Diabetic Activity

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Technology description

Technical Summary

Insulin is an important hormone in maintaining glucose homeostasis by coordinating the glucose absorption in peripheral tissues and hepatic glucose production. The action of insulin is initiated by binding to its cognate receptor (IR) and activation of the receptor's intrinsic protein tyrosine kinase activity. Impairment of components in this tyrosine kinase pathway often leads to disorders like diabetes mellitus (DM), a metabolic disease that may be characterized by chronic hyperglycemia and progressive β -cell failure with insufficient insulin output.

The diminution of pancreatic β -cell function is the major reason for all type-1 diabetes (T1D) and can exacerbate the condition of type-2 diabetes (T2D) patients. As a result, maintaining sufficient circulating insulin represents the primary goal in treating DM. Currently, the management of DM focuses on glucose control via lowering of blood glucose and hemoglobin A1c (HbA1c) with various pharmacological agents or insulin injections. Despite its relative effectiveness, subcutaneous insulin injection has suffered from drawbacks including tissue irritation, infection at injection sites, inconvenience and variation of insulin delivery rate. Therefore, the identification of orally active small molecules that are able to mimic insulin's effect might lead to a better therapy for DM patients. Emory researchers, led by Dr. Keqiang Ye, have identified a small, nonpeptidyl molecule that acts as an insulin mimetic by selectively activating IR but not the insulin-like growth factor receptor or other receptor tyrosine kinases. This compound sensitizes insulin's actions in provoking the activation of IR and its downstream signaling cascades. It also strongly elevates glucose uptake in adipocytes. Oral administration of this compound significantly lowers blood glucose in diabetic mice models. Diabetes affects nearly 170 million people worldwide, with the WHO predicting 300 million diabetics by 2025. Total diabetes market is ~\$20 billion.

Advantages

Circulating blood glucose in normoglycemic and hyperglycemic mice was significantly decreased to 70% of basal level 3 ~ 4 h after a single oral administration of 5 mg/kg.

Institution

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