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Mild blockade of Kv2.1 channel potentiates GLP-1's insulinotropic effects in islets and reduces its doses required for improving glucose tolerance in type 2 diabetic male mice

生理学講座統合生理学部門の大学院生 Rauza Sukma Rita 氏、出崎克也准教授、矢田俊彦教授らは、食事により腸から放出されてインスリン分泌を促進する消化管ホルモン Glucagon-like peptide-1（GLP-1）の膵β細胞の受容体シグナルに電位依存性 Kv2.1 チャネルが関与しており、Kv2.1 チャネルのわずかな阻害により GLP-1 作用の感受性が亢進し、低濃度の GLP-1 アナログによってインスリン分泌が大きく増大することを発見しました。その研究成果が Endocrinology (2015;156:114-123) 誌に報告されましたので、Rita 氏と矢田教授に研究の意義と経緯を伺いました。

Q1. What is background of this study?

Glucagon-like peptide-1 (GLP-1), a physiological incretin hormone, is secreted from the intestinal L cells in response to meals and enhances insulin release to maintain normoglycemia. Circulating GLP-1 is rapidly degraded by dipeptidyl peptidase-4 (DPP-4) with a half-life around 1-2 minutes. Currently, chemically modified DPP-4-resistant GLP-1 agonists and DPP-4 inhibitors have been clinically used for treating type 2 diabetic patients. They show lesser risk of causing hypoglycemia than other anti-diabetic drugs, sulphonylureas and glynides. However, nausea and vomiting have been documented as the common adverse events of GLP-1 agonists. A practical way to reduce these side effects is to lower their doses. This could be achieved by combining other substance or mechanism that can collaborate with GLP-1 agonists on insulin release.

Q2. What is function of Kv2.1 channel in pancreatic β-cells?

In pancreatic β-cells, glucose metabolism-induced closure of ATP-sensitive K^+ (K_{ATP}) channels and membrane depolarization open the voltage-dependent Ca^{2+} channels, triggering Ca^{2+} influx and insulin secretion. In parallel, glucose-induced depolarization also activates voltage dependent potassium (Kv) channel, thereby repolarizing β-cells. Among Kv channel families, Kv2.1 channel is the major component of Kv currents in rodent. Studies with the pharmacological Kv2.1 blockers and Kv2.1 knockout mice have suggested that this channel physiologically limits glucose-induced insulin secretion in β-cells. Since the β-cell Kv channels are open only when β-cells are depolarized by elevated glucose, blockade of Kv2.1 channels in β-cells could promote insulin release only at elevated glucose, causing lower risk of hypoglycemic events compared to the K_{ATP} channel blockers. Furthermore, inhibition of Kv2.1 channels is expected to enhance the GLP-1 action on islet β-cells and facilitate GLP-1-based therapy since GLP-1 reportedly attenuates β-cell Kv channel.

Q3. What are results until now?

This study aimed to determine whether pharmacological or genetic blockade of Kv2.1 channels potentiates insulinotropic effect of GLP-1 agonists. GLP-1 receptor agonist exendin-4 (Ex-4) and Kv2.1 channel blocker guangxitoxin-1E (GxTx) at sub-threshold concentrations, when combined, markedly increased insulin release and cytosolic Ca^{2+} concentration ($[Ca^{2+}]_i$ in a glucose-dependent manner in mouse islets and β-cells. Ex-4 at sub-threshold concentration alone increased islet insulin release and β-cell $[Ca^{2+}]_i$ in Kv2.1$^{+/-}$ mice. The $[Ca^{2+}]_i$ response to sub-threshold Ex-4 and GxTx in combination was attenuated by pretreatment with protein kinase-A (PKA) inhibitor H-89, indicating PKA-dependency of the cooperative effect. These results indicate that GLP-1 agonist and Kv2.1 channel blocker act synergistically to activate β-cells and induce insulin secretion. Furthermore, sub-threshold doses of GxTx and GLP-1 receptor agonist liraglutide in combination markedly increased plasma insulin and improved glucose tolerance in diabetic db/db mice and NSY mice. These results indicate that Kv2.1 channels physiologically limit insulinotropic actions of GLP-1.

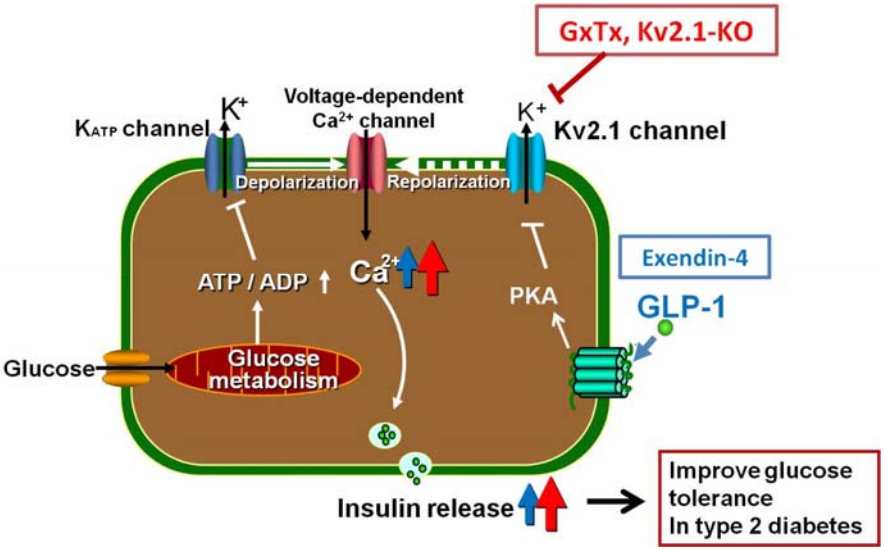

Figure 1. Blockade of Kv2.1 channel by Kv2.1 channel blocker guangxitoxin (GxTx) and Kv2.1$^{+/-}$ mice potentiates GLP-1-induced insulin release in pancreatic islet β-cells and improves glucose tolerance in type 2 diabetes.

Q4. What is a benefit of this study?

This study demonstrates that combination of low doses of GLP-1 agonist and Kv2.1 channel blocker had strong *in vivo* insulinotropic and blood glucose-lowering effects in type 2 diabetic mice. Blockade of Kv2.1 channels enhances potency of GLP-1-based drugs, which can lower their dose required to improve glucose tolerance in type 2 diabetes and thereby reduce the frequency of their adverse effects.

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