GS01-1 **Regulation of insulin secretion through DAG phosphorylation by type-1 DGK in pancreatic beta-cells**

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In type-2 diabetes, excessive diacylglycerol (DAG) accumulation in pancreatic β-cells has been shown to lead to the insufficiency of insulin secretion. Thus, the regulation of intracellular DAG levels, which are strictly controlled by DAG kinase (DGK), is expected to be important to maintain β-cell function. We have previously shown that DAG accumulation resulting from dysfunction of DGK α and γ, type-1 DGK isoforms, reduces insulin secretion. In the present study, we investigated the mechanism of suppression of insulin secretion due to type-1 DGK dysfunction in β-cells and its contribution to type-2 diabetes. The amplitude of glucose-induced intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) oscillations was increased by low concentrations of R59949, a type-1 DGK inhibitor, and DiC_8, a DAG analog. These effects were abolished by Ro31-8220, a protein kinase C inhibitor. In contrast, high concentrations of R59949 and DiC_8 suppressed glucose-induced $[Ca^{2+}]_i$ elevation, which was insensitive to Ro31-8220, and reduced voltage-dependent Ca^{2+}(VDCC) currents. Moreover, low concentrations of R59949 and DiC_8 potentiated glucose-stimulated insulin secretion, whereas high concentrations of R59949 suppressed it. The expression of DGK α and γ was lower in the type-2 diabetes model NSY mice. These results suggest that DAG accumulation due to type-1 DGK dysfunction has contradictory dual effect in β-cells depending on the degree of DAG accumulation. Type-1 DGK is expected to be a key molecule for the progression of type 2 diabetes.