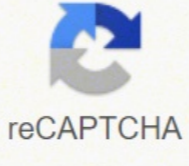


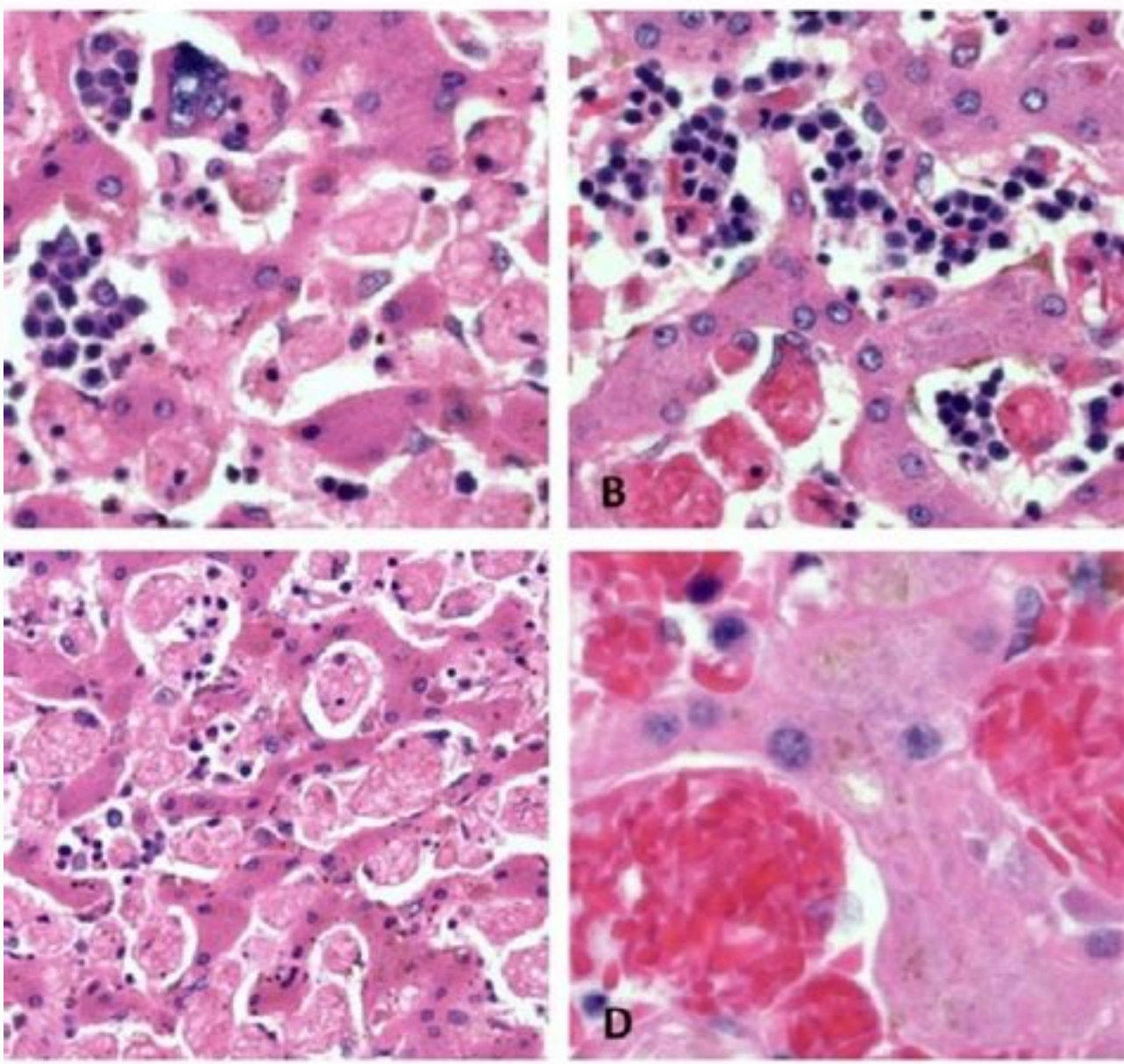
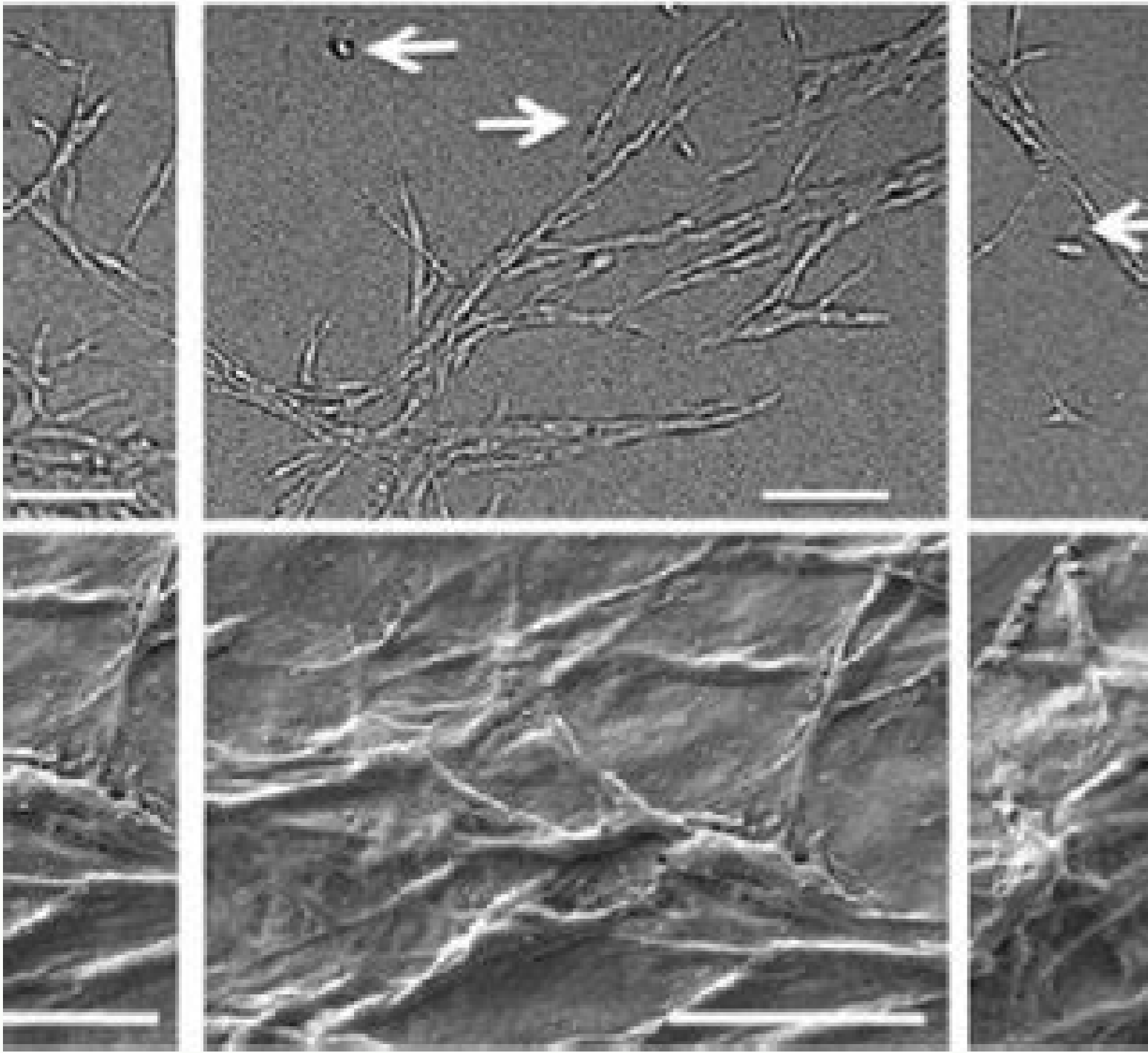


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ORIGINAL ARTICLE

Distinct effects of dipeptidyl peptidase-4 inhibitor and glucagon-like peptide-1 receptor agonist on islet morphology and function

Anika Morita¹, Eri Mukai¹, Ayami Hiratsuka¹, Tomonori Taketani¹, Toshiko Iwama², Eun Young Lee³, Takashi Miki⁴

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Abstract Although the two anti-diabetic drugs, dipeptidyl peptidase-4 inhibitors (DPP4is) and glucagon-like peptide-1 (GLP-1) receptor agonists (GLP1RAs), have distinct effects on the dynamics of circulating insulin, little is known of the difference in their consequences on morphology and function of pancreatic islets. We examined these in a mouse model of β cell injury/regeneration. The model mice were generated to express dipeptidyl toxin (DT) receptor and a fluorescent protein (Tomato) specifically in β cells. The mice were treated with a DPP4i (MK-0626) and a GLP1RA (liaglutide), singly or doubly, and the morphology and function of the islets were compared. Prior administration of MK-0626 and/or liaglutide similarly protected β cells from DT-induced cell death, indicating that enhanced GLP-1 signaling can account for the cytoprotection. However, 2-week intervention of MK-0626 and/or liaglutide in DT-injected mice resulted in different islet morphology and function: β cell proliferation and glucose-stimulated insulin secretion (GSIS) were increased by MK-0626 but not by liaglutide, a cell mass was decreased by liaglutide but not by MK-0626.

Although liaglutide administration nullified MK-0626-induced β cell proliferation, their co-administration resulted in increased GSIS, decreased α cell mass, and improved glucose tolerance. The pro-proliferative effect of MK-0626 was lost by co-administration of the GLP-1 receptor antagonist exendin-9-39, indicating that GLP-1 signaling is required for this effect. Comparison of the effects of DPP4is and/or GLP1RAs treatment in a single mouse model shows that the two anti-diabetic drugs have distinct consequences on islet morphology and function.

Keywords DPP-4 inhibitor · GLP-1 receptor agonist · β cell proliferation · Apoptosis · Insulin secretion · Glucose tolerance

Introduction

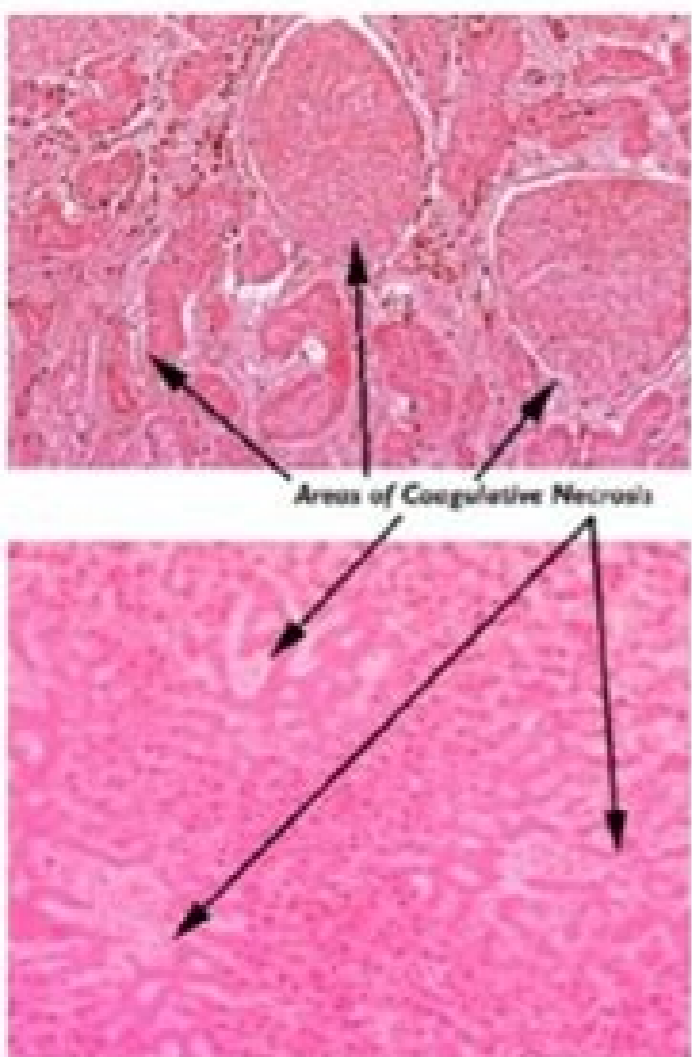
Type 2 diabetes mellitus (T2DM) is a metabolic disorder characterized by chronic hyperglycemia. Defective insulin secretion from pancreatic β cells and/or defective insulin action in peripheral tissues contributes to its development [1]. Numerous insulin secretagogues (such as sulfonylureas and glinides) and insulin sensitizers (such as biguanides and thiazolidinediones) have been used for the treatment of T2DM [1]. However, several large human clinical trials have revealed that none of these oral anti-diabetic drugs can afford long-lasting, glycemic control [2, 3]. In most patients with T2DM, glycemic control usually deteriorates over time, together with a progressive decline in β cell function [4].

β cell mass of T2DM patients has also been shown to be decreased compared with that of normal subjects, as assessed by cadaveric or operatively extracted specimens [5–8]. Notably, β cell mass is known to decline

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Coagulative necrosis in two organs: Kidney (TOP) and Liver (Bottom). Note preservation of tissue architecture. Some relatively normal liver cells survive, in which nuclei are visible.

definitions

- Cell injury
- Cellular adaptation
- Reversible cell injury
- Irreversible cell injury
- Apoptosis
- Autophagy
- Cell death
- Cellular injury
- Cellular adaptation
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