Metformin perturbs pancreatic differentiation from human embryonic stem cells

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Abstract:
Metformin is becoming a popular treatment before and during pregnancy but current literature on *in utero* exposure to metformin lacks long-term clinical trials and mechanistic studies. Current literature on the effects of metformin on mature pancreatic β cells highlighted its dual, opposing, protective or inhibitory, effects depending on metabolic environments. However, the impact of metformin on developing human pancreatic β cells remains unknown. Here, we investigated the potential effects of metformin exposure on human pancreatic β cell development and function *in vitro*. In the absence of metabolic challenges such as high levels of glucose and fatty acids, metformin exposure impaired the development and function of pancreatic β cells, with downregulation of pancreatic genes and dysfunctional mitochondrial respiration. It also affected the insulin secretion function of pancreatic β cells. These findings call for further in-depth evaluation of the exposure of human embryonic and fetal tissue during pregnancy to metformin, and its implications on long-term offspring health.

Figure:

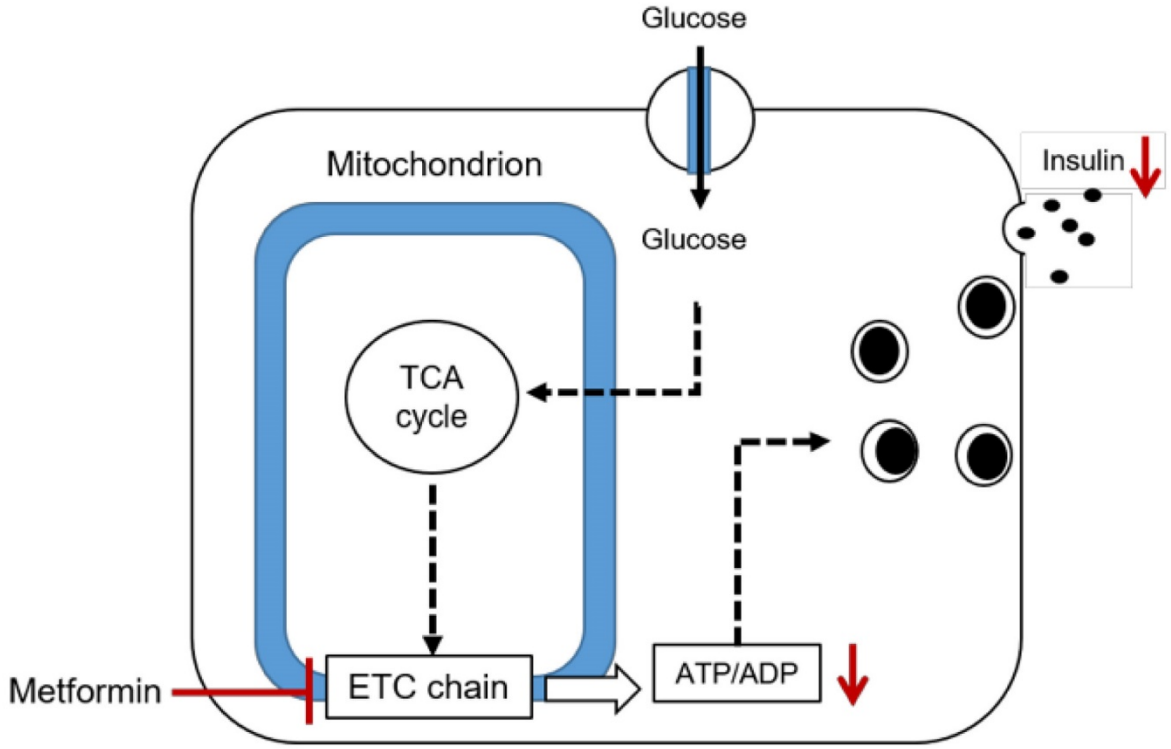

Figure legend: Model depicting the effects of metformin on hESC-derived pancreatic β-like cells and pancreatic β cells

Metformin decreases mitochondrial respiration in pancreatic β-like cells by affecting genes in the electron transport chain (ETC), leading to decreased ATP production. These changes in turn result in reduced insulin expression and insulin secretory function in response to a glucose challenge.