論文の内容の要旨

Mathematical modeling of plasma glucose homeostasis regulated by plasma insulin in humans

（数理モデルを用いたヒト血糖値恒常性制御システムの解析）

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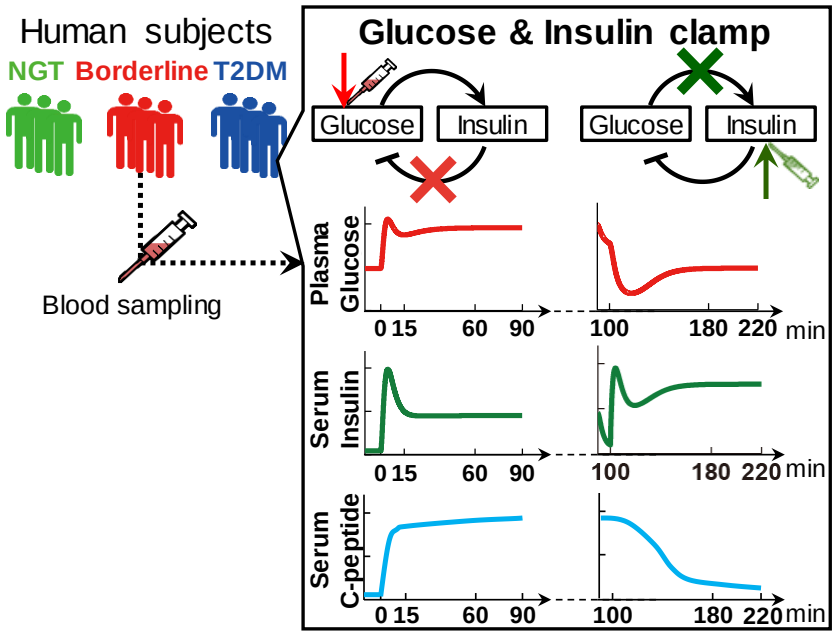
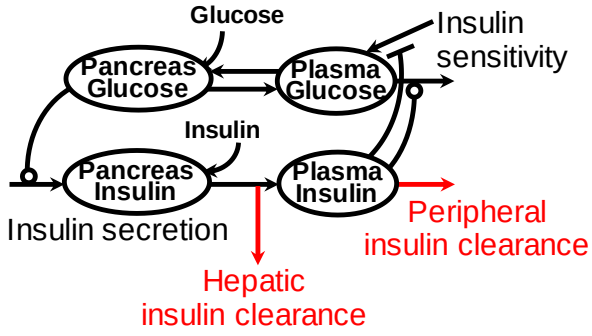
Plasma glucose concentration is regulated to be constant, known as glucose homeostasis, by a complex feedback between circulating glucose and insulin, of which failure leads to type 2 diabetes mellitus (T2DM). The feedback loop is characterized by the abilities of insulin secretion promoted by glucose and glucose uptake promoted by insulin, known as insulin sensitivity. Plasma insulin concentration is affected by insulin clearance ability, which consists of hepatic removal from portal vein and peripheral removal from systemic circulation. However, it is difficult to assess these abilities of body tissues directly from the circulating insulin measurement because of the negative feedback between circulating glucose and insulin. In this study, I developed two kinds of mathematical models based on the consecutive hyperglycemic and hyperinsulinemic-euglycemic clamp analysis performed for 121 subjects including healthy and T2DM. First, I generated the models reproducing the observed time courses of plasma

glucose and insulin concentration for specifically quantifying these abilities of insulin secretion, sensitivity, and clearance by accounting for the negative feedback. It was found that peripheral insulin clearance significantly decreased from healthy to T2DM during the progression of glucose intolerance. However, these models did not distinguish the hepatic and peripheral insulin clearance explicitly. Second, I reported another type of models reproducing the time courses of plasma insulin and C-peptide concentrations for separately quantifying hepatic and peripheral insulin clearance as the difference between pre-hepatic and post-hepatic insulin concentrations. An increase in hepatic but a decrease in peripheral insulin clearance from healthy to T2DM were found, respectively. The model analysis revealed that hepatic and peripheral insulin clearance affected the dynamics of amplitude and temporal patterns, respectively. These results suggest that those two insulin clearance play essential and different roles in regulating plasma insulin concentration and glucose homeostasis.

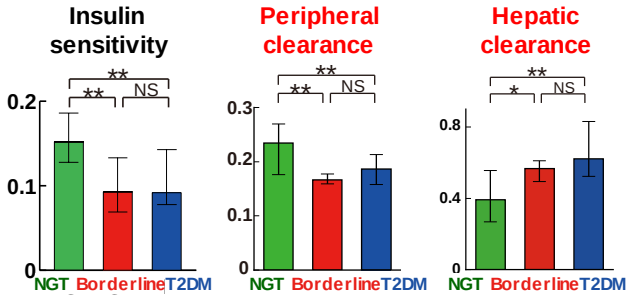
Summary figure



Mathematical model



Parameters reflect progression of T2DM



Temporal patterns of serum insulin concentration