論文の内容の要旨

論文題目

The Selective Control of Glycolysis, Gluconeogenesis and Glycogenesis in Glucose Metabolism by Temporal Insulin Pattern

（インスリンの時間パターンはグルコース代謝における解糖系、糖新生、グリコーゲン合成を選択的に制御する）

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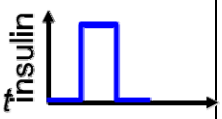
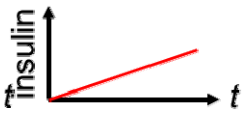
The temporal changes and absolute concentrations of insulin selectively govern systemic glucose metabolism, including the glycolysis, gluconeogenesis and glycogenesis pathways. However, the mechanisms by which the insulin-signalling pathway selectively regulates glycolysis, gluconeogenesis and glycogenesis remain to be elucidated. To address this issue, we experimentally measured changes in the concentrations of the metabolites in glucose metabolism in response to insulin. An insulin step stimulation induced a transient response in the glycolysis and glycogenesis pathways and a sustained response in the gluconeogenesis pathway and the extracellular glucose concentration. Based on the experimental results, we constructed a simple computational model that characterises the responses of insulin signalling-dependent glucose metabolism. The model revealed that the network motifs of the glycolysis and

glycogenesis pathways constitute a feedforward with substrate depletion and an incoherent feedforward loop (Figure 1), respectively, which enable glycolysis and glycogenesis to respond to temporal changes in the insulin level rather than to the absolute concentration of insulin (Table 1). In contrast, the network motifs of the gluconeogenesis pathway constituted a feedforward inhibition (Figure 1), which makes the gluconeogenesis pathway responsive to the absolute concentration of insulin, regardless of its temporal pattern (Table 1). The extracellular glucose concentration was regulated by gluconeogenesis and glycolysis. These results demonstrate the selective control mechanism of glucose metabolism by temporal insulin patterns.

Table I. Insulin selectively controls glycolysis, gluconeogenesis, glycogenesis and the extracellular glucose concentration via their network motifs.

	Network Motifs	Step 	Pulse  Additional secretion-like	Ramp  Basal secretion-like
Glycolysis (F16P)	FF with SD	+ Adaptation	+	-
Gluconeogenesis (PEPCK)	FF	+	+	+
Glycogenesis (Glycogen)	iFFL	+ Adaptation	+	-
Extracellular glucose concentration (GLC_{ex})		+	+	+

A high responsiveness to the indicated stimulations is represented by “+”, and a low responsiveness is represented by “-”.

Abbreviations: FF with SD, feedforward with substrate depletion; FF, feedfoward; iFFL, incoherent feedforward loop.

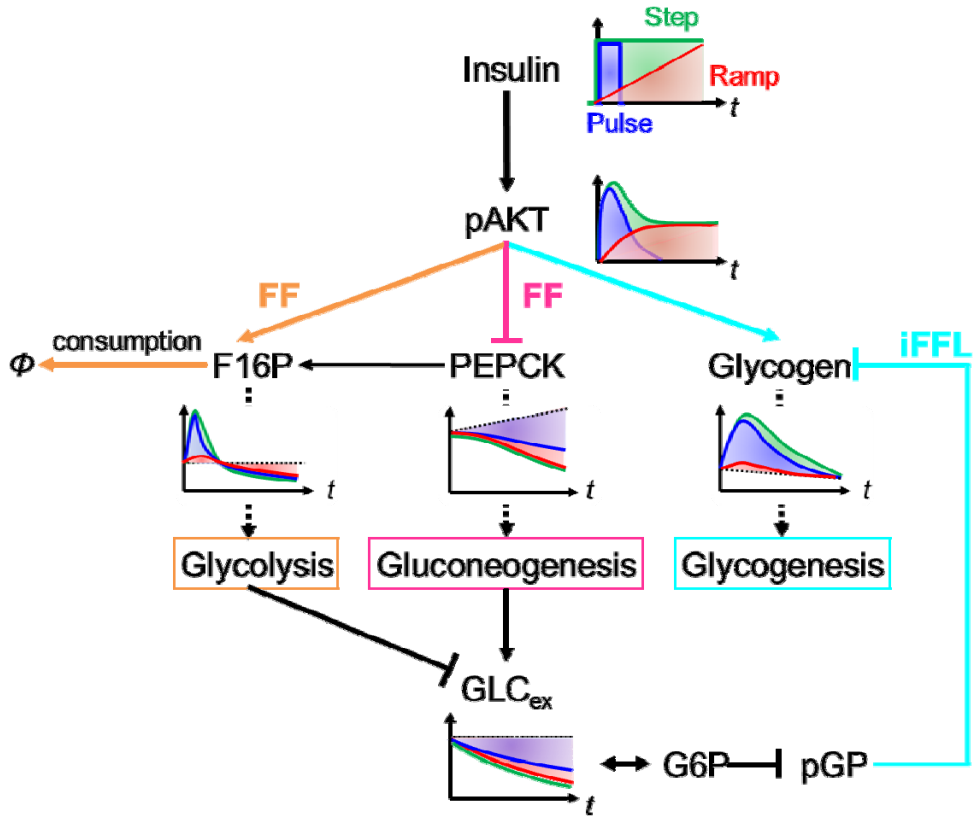


Figure 1. Selective control mechanisms of the glycolysis, gluconeogenesis and glycolysis in the insulin-dependent glucose metabolism model.

The responses of pAKT, F16P, PEPCK, glycogen and GLC_{ex} to step (green), pulse (blue) and ramp (red) stimulations with insulin are shown. Glycolysis (F16P) responds to temporal insulin changes (step and pulse stimulations) via feedforward (FF) activation and substrate depletion (orange). Gluconeogenesis (PEPCK) responds to the absolute insulin concentration (step, pulse and ramp stimulations) via feedforward (FF) inhibition (pink). Glycogenesis (glycogen) responds to temporal insulin changes (step and pulse stimulations) via an incoherent feedforward loop (iFFL) (cyan). GLC_{ex} responds to all insulin stimulations via gluconeogenesis and glycolysis.