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COMMENTARY

Novel mechanism of impaired metabolism-secretion coupling in β-cells: Loss of cytosolic adenosine triphosphate by leakage

Glucose-specific impairment of insulin secretion is a characteristic of type 2 diabetes. Results from experiments using diabetic rodent and human islets show that decreased glucose-stimulated insulin secretion in diabetes is caused, at least in part, by impaired metabolism-secretion coupling in β-cells. In turn, impaired glucose metabolism and adenosine triphosphate (ATP) production in β-cells causes a decrease in glucose-stimulated insulin secretion[1]. Indeed, dysregulation of glucose metabolism in diabetic islet cells occurs during the early stages of β-cell deterioration before late-stage events, including inflammation, fibrosis, decreased exocytosis and apoptosis, can occur[2]. Therefore, impaired metabolism-secretion coupling might play important roles in the pathogenesis and mechanism of β-cell dysfunction in type 2 diabetes.

In the Goto-Kakizaki (GK) rat, a genetic model of type 2 diabetes mellitus, glucose-induced insulin secretion is selectively impaired. The intracellular ATP elevation induced by high glucose is also impaired in islets from both GK rats and patients with type 2 diabetes. The impaired insulinotropic action of glucose in the β-cells of GK rats might be attributable to insufficient closure of the K_{ATP} channels as a result of deficient ATP production derived from impaired glucose metabolism[1,3]. Activity of mitochondrial glycerol phosphate dehydrogenase, the key enzyme in the glycerol phosphate shuttle, is reduced in islet cells from GK rats and patients with type 2 diabetes. Impairment of ATP production and metabolism-secretion coupling in β-cells is caused by endogenous overproduction of reactive oxygen species (ROS) involving Src activation (Figure 1)[1]. In addition, a Warburg-like effect, the characteristic aerobic metabolism in cancer cells by which lactate is overproduced with reduced mitochondrial metabolism, plays an important role in impaired metabolism-secretion coupling in diabetic β-cells. The presence of this phenomenon suggests that ROS reduction can improve mitochondrial metabolism by suppressing lactate overproduction through inhibition of hypoxia-inducible factor-1α[4]. These events are consistent with the recent temporal transcriptomic and proteomic evaluation of metabolism in GK islet cells, in which upregulation of glycolysis, downregulation of Krebs cycle, downregulation of glycerol phosphate shuttle and upregulation of anti-oxidants against ROS overproduction were observed[2].

Zhang *et al.*[5] recently proposed a new mechanism of metabolism-secretion coupling impairment in diabetic β-cells involving the loss of cytosolic ATP by leakage through plasma membrane (Figure 2). Hyperglycemia increases the expression of the ATP-conducting mitochondrial outer membrane voltage-dependent anion channel-1 (VDAC1) and its mistargeting to the β-cell surface. VDAC1 expression on the plasma membrane leads to ATP depletion and impaired insulin secretion. VDAC1 inhibitors, including metformin, restore insulin secretion in islet cells of patients with type 2 diabetes, and prevent hyperglycemia in diabetic mice. As VDAC1 is not only permeable to ATP, but also to creatine phosphate, HPO_4^{2-}, and succinate[6], ATP production might also be impaired by VDAC1 overexpression, consistent with the reduced oxygen consumption rate in this condition.

Metformin, a synthetic biguanide, is currently one of the most frequently used oral hypoglycemic agents for type 2 diabetes around the world. The agent has been considered to act mainly on the liver and suppress endogenous glucose production, including gluconeogenesis and glycogenolysis. As metformin is hydrophilic, the expression of organic cation transporters is necessary to act on its intracellular molecular targets. Macini *et al.*[7] reported that human islets cultured with high glucose showed a reduced glucose-stimulated insulin secretion that was associated with a lower ATP : adenosine diphosphate ratio, and these functional defects are recovered by the presence of metformin in culture medium. However, molecular targets of metformin in direct effects on β-cells remained unknown, as expression levels of organic cation transporter 1 and organic cation transporter 2, which are expressed mainly in the liver and kidney, respectively, are very low in β-cells. Zhang *et al.*[5] showed that metformin directly inhibits conductance of VDAC1, which is reconstituted in planar lipid bilayers, and that metformin restores impaired glucose-induced insulin secretion and elevation of ATP content in *db*/*db* mice islets and in type 2 diabetes islets, in both of which overexpression of VDAC1 causes its mistargeting to the plasma membrane.

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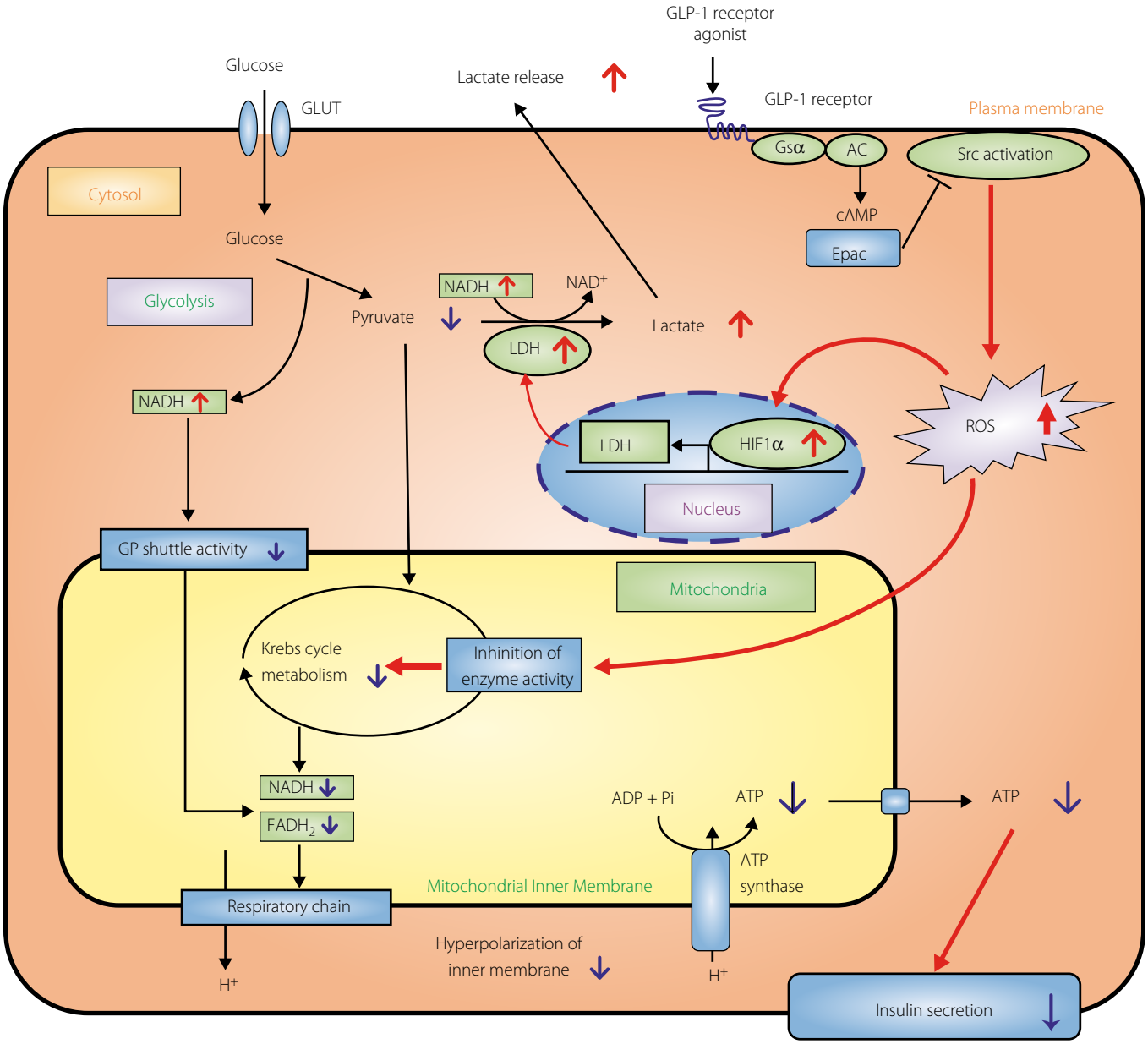

Figure 1 | Impaired metabolism-secretion coupling in diabetic Goto-Kakizaki rat β-cells. AC, adenylate cyclase; ADP, adenosine diphosphate; ATP, adenosine triphosphate; $FADH_2$, reduced flavin adenine dinucleotide; GLP-1, glucagon-like peptide-1; GLUT, glucose transporter; GP shuttle, glycerol phosphate shuttle; Gsα, stimulatory heterotrimeric G protein α subunit; HIF1α, hypoxia-inducible factor 1α; LDH, lactate dehydrogenase; NAD, oxidized nicotinamide adenine dinucleotide; Pi, inorganic phosphate; NADH, reduced nicotinamide adenine dinucleotide; ROS, reactive oxygen species.

In clinical settings, treatment to improve hyperglycemia often at least partially causes the recovery of glucose-induced insulin secretion in patients with type 2 diabetes. This reversible impairment of insulin secretion is often considered as glucotoxicity on β-cells (or β-cell exhaustion). Elucidating the clinical relevance of VDAC1 overexpression in glucose toxicity on β-cells might contribute to a more profound understanding of diabetes pathophysiology.

Zhang *et al.*[5] also showed that glucotoxicity-induced VDAC1 induction is thioredoxin-interacting protein-dependent. The interaction between ROS overproduction and VDAC1 induction is an interesting issue to be resolved for the following reasons: (i) ROS overproduction is an early event during β-cell deterioration[2]; (ii) although glucose, sensed by MondoA:Mlx complexes, can directly induce the expression of thioredoxin-interacting protein[8], ROS induce the

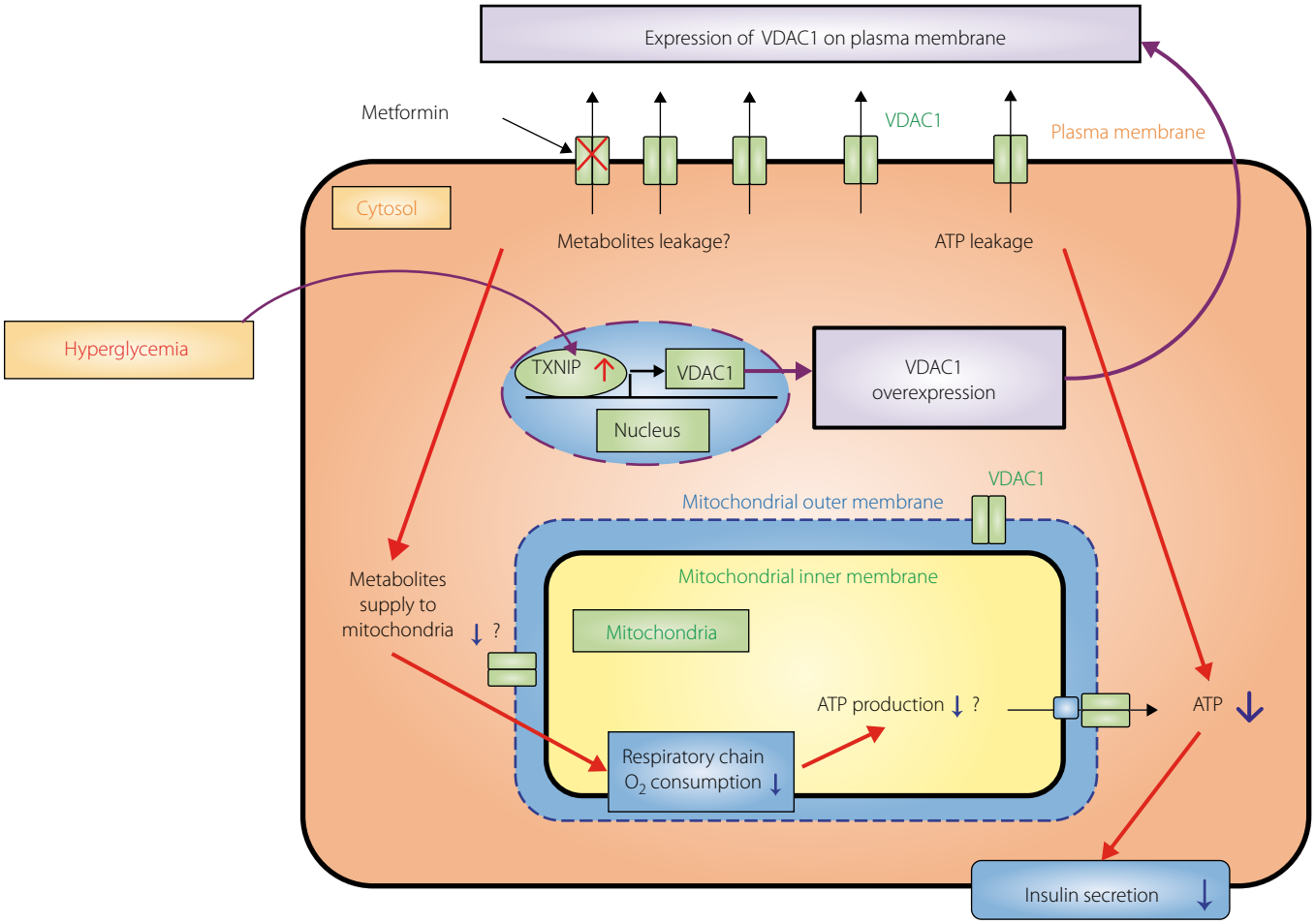

Figure 2 | Impaired metabolism secretion coupling caused by voltage-dependent anion channel 1 (VDAC1) overexpression. ATP, adenosine triphosphate; TXNIP, thioredoxin-interacting protein.

dissociation of thioredoxin-interacting protein from thioredoxin, and increase its recruitment to interact with other proteins[9]; and (iii) glucotoxicity eventually results in the accumulation of intracellular ROS through several pathways[10]. This elucidation will contribute to the comprehensive understanding of the mechanism behind impaired metabolism-secretion coupling in type 2 diabetes.

DISCLOSURE

The author declares no conflict of interest.

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