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COMMENTARY

Commentary: Inhibitors of mitochondrial respiratory chain in the treatment of type 2 diabetes

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Prevalence of type 2 diabetes has been increased worldwide following the high incidence of obesity and growing population of aging, which are two conditions for absolute energy excess with accumulation of TAG in the body and relative energy excess due to reduced energy expense, respectively. It appears that type 2 diabetes is a compensatory mechanism of body to energy excess through urine discharge of glucose. This view based on energy homeostasis provides a simple link between type 2 diabetes and obesity/aging. However, there is no consensus yet about the cellular and molecular mechanisms of insulin resistance, which is responsible for hyperglycemia and glucose urine in type 2 diabetes. Ten years ago, mitochondrial overheating is suggested as a mechanism of insulin resistance in a review article in this journal by a conclusion that mitochondrial inhibitors are able to improve insulin sensitivity[1].

In the past ten years, new evidence has emerged to support the role of inhibitors of mitochondrial respiratory chain in the improvement of insulin sensitivity. Mitochondria are extensively investigated in the pathogenesis of type 2 diabetes for its close relationship to insulin resistance[2,3]. However, it is generally believed that mitochondrial dysfunction is a cause of insulin resistance[2,3], which is opposite to the view of mitochondrial overheating[4]. Mitochondrial overheating is a concept in the pathogenesis of insulin resistance in obesity. Mitochondria are subject to active adaptation to energy metabolism with functional and structural changes in the physiological conditions including both energy surplus and energy deficit[5]. In the energy surplus conditions, substrate overloading occurs in mitochondria to trigger mitochondrial overheating, which is defined as excess production of ATP over the cellular demand[4]. The concept has been used to explain several pathological changes in obesity, such as hyperinsulinemia and hyperglucagonemia, in the mechanism of hyperglycemia in type 2 diabetes. ATP oversupply in insulin-producing cells (pancreatic β-cells) is a primary cause of hyperinsulinemia, and ATP oversupply in glucagon-producing cells (pancreatic α-cells) is responsible for

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hyperglucagonemia[4]. ATP over production in insulin-sensitive cells (myotubes and adipocytes) explains the reduced AMPK activity in the type 2 diabetes. The substrate-driven ATP over-production is supported by the biochemical principle, transgenic studies, and pharmacological studies in variety of animal models[4]. More importantly, it gains a solid support from clinical studies of metformin, SGLT2 inhibitors and bypass surgeries, all of which improve insulin sensitivity by correction of mitochondrial overheating[1,4]. Mitochondrial inhibitors were considered as a new class of insulin sensitizers years ago[1], in which several inhibitors including metformin, berberine, TZD, resveratrol, and EGCG were discussed in the regulation of insulin sensitivity.

The mitochondrial respiratory chain is a major target of the inhibitors in insulin sensitization as demonstrated initially for metformin, the first-line of medicine in the clinical treatment of type 2 diabetes. Metformin has several targets in mitochondria[6], which include the complex I[6], complex IV[7] and complex V[6] in the respiratory chain. The inhibitory activity was observed at millimolar concentrations *in vitro* 20 years ago and significance of the observation was challenged for the clinically non-relevant concentrations of millimolar[6]. Metformin concentrations are at micromolar levels in the patient plasma under therapeutic dosages. However, metformin does reach the millimolar concentration in the gut where about 50% metformin is not absorbed into the blood circulation[8]. In the gut cells, metformin may inhibit the mitochondrial complex through a direct interaction with the respiration complex proteins[9]. The activity may apply to metformin modulation of gut microbiota of diabetic patients for improvement of insulin sensitivity[10]. Bacteria has respiratory chain although they lack a structure of mitochondria. In addition to mitochondria, metformin may target lysosome in the improvement of insulin sensitivity through activation of AMPK[11]. The major side effect of metformin is gastro-intestine responses and its built-up in the blood stream in patients with kidney failure.

The metformin activity gains new support in a recent study of sterol structure of the complex I[9]. The concept of complex I inhibition is able to explain the broad activities of metformin in cells, such as activation of AMPK, induction of mitophagy and AMPK-independent activity[6,12–14]. However, the structural basis was missing for the metformin activity for a long time. This issue is resolved in the recent study by Bridges et al.[9] that is published in the journal *Science*, in which the molecular structure of mammalian complex I was investigated for the metformin interaction. The study provides the molecule evidence of metformin interaction with the complex I and also a mechanism of the low toxicity of metformin. In the study, IM1092, a more hydrophobic derivative of the metformin-related antidiabetic biguanide phenformin, was employed instead of metformin itself. In the study, IM1092 was compared with rotenone, a classical chemical inhibitor of complex I, in cellular toxicity[15]. The low toxicity of IM1092 was attributed to a self-limitation activity of the chemical upon entrance into mitochondria, which avoids unreversible inhibition of the respiratory chain in the toxicity. The study provides new support to the metformin activity in the inhibition of mitochondrial respiration.

In this line, other inhibitors of the mitochondrial respiratory chain including berberine and sennoside A prevent mitochondrial overheating in the large intestine in the preservation of GLP-1 secretion function of L-cells in the obese mice[16,17]. Berberine may prevent mitochondrial swelling in the skeletal muscle in the intralipid-induced insulin resistance model for improvement of insulin sensitivity[18]. These activities of berberine are related to its inhibitory activity of complex I in the mitochondrial respiratory chain[19]. Additionally, inhibition of the complex I by rotenone, amobarbital and NDUFA13 (NADH dehydrogenase[20] 1 a subcomplex subunit 13) gene silence all improves insulin sensitivity in mice[21]. These inhibitors together with metformin provide new support to the concept of mitochondrial overheating in the mechanism of insulin resistance.

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