Diabetes Mellitus: could the Inhibition of a Single Enzyme (CPT-1) Involved in the Beta-Oxidation Process Improve this Complex Disease?

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Abbreviations: NIDDM: Non-Insulin-Dependent Diabetes Mellitus, FFA: Free-Fatty Acid; TG: Triglyceride

Letter to Editor

Diabetes mellitus is a heterogeneous chronic disease characterized by hyperglycemia, and insulin resistance. The causes lie the interaction of genetic and environmental factors that occur with deficiency in production of insulin by the pancreas, or by ineffectiveness of insulin produced.

Diabetes mellitus is among ten leading cause of death in high-income countries and it is increasing rapidly in countries undergoing industrialization. Diabetes alone claims on the average around 8% of total health budgets in developed countries [1]. Complications include diabetic retinopathy, renal failure, heart disease, diabetic neuropathy and foot ulceration and amputation. More than 90% of diabetic patients in the United States are Type 2 diabetics, or non-insulin-dependent diabetes mellitus (NIDDM). In NIDDM a severe glycemic control should be made by a synergic work of physical activity, diabetic diet, and the use of hypoglycemic agents, and lastly insulin.

Current hypoglycemic therapies are continuously ongoing, but not sufficiently adequate to control hyperglycemia, due to their side effect that discontinuous the treatment in the patients. It is possible distinguish different types of hypoglycemic agents: sulphonylureas (insulin secretagogues), biguanide, like metformin (insulin sensitizer and hepatic glucose production inhibitor), “glitazones” (insulin sensitizers), α-glucosidase intestinal inhibitors (acarbose), meglitinides (glinides) (post prandial hypoglycemic agent) and ultimate metabolic hormones: GLP-1 receptor agonists (incretin mimetics) and DPP-4 inhibitors, both members of the glucagon peptide superfamily.

In the last decades, another pathway was tested in NIDDM to keep glycaemia and insulin resistance under control, I mean the way of limitation of mitochondrial fatty acid oxidation by CPT inhibition. It is known that fatty acids oxidation stimulates liver production of glucose, which is an important factor in diabetic hyperglycemia. The mechanism through which fatty acid oxidation stimulates hepatic glucose neo-synthesis is essentially by activation of pyruvate carboxylase in the mitochondrial matrix which requires acetyl-CoA, a major product of mitochondrial beta-oxidation of long-chain fatty acids, as activator to catalyzes the thermodynamically irreversible reaction, which is the rate limiting in hepatic gluconeogenesis [2].

In the past years, several approaches were attempted to inhibit the fatty acid oxidation pathway indirectly by inhibiting substrate release (fatty acids) from adipose tissue [3]. These approaches were unsuccessful because of side effects and/or lack of efficacy. Therefore, a different strategy was developed: the idea was to modulate liver fatty acid oxidation through the inhibition of the carnitine-dependent transfer of fatty acid from the cytosol to the mitochondrial matrix, where beta-oxidation occurs. Since beta-oxidation occurs in mitochondria, and fatty acids per se cannot pass the inner mitochondrial membrane, an important rate-limiting step in beta-oxidation exist: the pivotal enzyme CPT (CPT1, outer and CPT2, inner mitochondrial membrane). Its blockade can significantly reduce both the beta-oxidation and glucose synthesis. Consequently, the inhibition of hepatic CPT1 can be considered an efficacious strategy in the therapy of diabetes, furthermore the condition of insulin...
resistance is evidenced by over-production of glucose in liver and under-utilization of glucose in muscle [4]. In addition, in NIDDM patients not adequately treated, increased gluconeogenesis was shown to be one of the major factors responsible for fasting and post-absorptive hyperglycemia [5].

Experimental observations of Jenkins and Griffith [6] showed the possibility of using DL-aminocarnitine a sliver CPT1 inhibitor. Infact, a strong hypoglycemic effect in fasted diabetic mice treated with a single dose (0.3 mmol/kg) was found plasma glucose levels normalized within 4-8 hours and remaining effective for at least 12 hr. However, in the previous experiment [7] when were administered a single dose (5 mmol/kg) of acetyl-DL-aminocarnitine in starved mice it was found seriously liver and kidney triglyceride levels very markedly elevated for up to 3 days. Another potent inhibitor of CPT1 was then applied in experimental condition to correct glycaemia: etomoxir, ethyl 2[(4-chloro-phenoxy)hexyl]oxirane-2-carboxylate [8].

A few years later, Hübinger, Weikert, Wolf & Gries published a paper [9] in which etomoxir were considered as "a new therapeutic approach in diabetes" by inhibition of CPT1. To support this claim, they administered etomoxir in 8 type 2 diabetic patients drawing a placebo-controlled, double-blind randomized study by using the euglycemic clamp technique. Results were: lowering plasma glucose levels without affecting plasma insulin concentrations, with an increase in plasma FFA and TG concentrations, suggesting that modulation of FFA metabolism at the level of adipocytes or of the liver can have dramatic effects on carbohydrate and lipid metabolism [9].

In a paper published in Diabetes, Reaven, Chang & Hoffman [10] in which etomoxir were considered as "a new therapeutic approach in diabetes" by inhibition of CPT1. To support this claim, they administered etomoxir in 8 type 2 diabetic patients drawing a placebo-controlled, double-blind randomized study by using the euglycemic clamp technique. Results were: lowering plasma glucose levels without affecting plasma insulin concentrations, with an increase in plasma FFA and TG concentrations, suggesting that modulation of FFA metabolism at the level of adipocytes or of the liver can have dramatic effects on carbohydrate and lipid metabolism [9].

Discussion about the use of etomoxir in diabetes and the possible role of CPT1 inhibition in improving glucose homeostasis, refreshing the interest in selective and reversible L-CPT1 inhibition as a potential antihyperglycemic approach.

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