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), “gliptazones” (insulin sensitzers), 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...
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A few years later, Hübinger, Weikert, Wolf & Gries published a paper [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: the mean metabolic clearance rate of glucose was raised while free fatty acids plasma levels, glucose counter regulatory hormones, lipids and C-peptide values were unaffected. Due to these hopeful results, the scientific community expected more papers published on diabetic patients treated and/or the product launch as oral hypo-glycemic agent.

The common element among the compounds above mentioned are irreversible inhibitors of CPT1 and they had not the selectivity of inhibition between two isoforms of CPT1, hepatic and cardiac, therefore, a greatest hitch in product development could be the accumulation of triglycerides in the heart (cardiac steatosis). To prevent this issue around the 2000s, it was proposed new compounds as potential antidiabetic agents able to perform that task [11].

In J Med Chem [12] we published a paper where we demonstrated in intact rat liver mitochondria the highest activity (IC\(_{50}\) = 0.7 microM) for a compound belonging to the derived class of "carnitine analogues with long alkyl chain". In enzymatic inhibition tests, carried out in liver and heart mitochondria this compound also showed a good selectivity (M-CPT1/L-CPT1 IC\(_{50}\) ratio = 4.86) for CPT1 between liver and heart isoform. This compound showed also a significant reduction of serum glucose levels in diabetic db/db mice treated orally. Another compound we tested in experimental diabetes, an ureidic derivative from class of "carnitine analogues with long alkyl chain". This ureidic compound, with extraordinarily high selectivity toward the liver CPT1 isoform with respect to the heart isoform was able to reduce serum glucose levels in diabetic db/db mice treated orally for 45 days at a dose of 50 mg/kg twice a day, showing also an antiketotic activity in normal fasted rats and therefore selected for development as a potential antiketotic and anti diabetic drug [13].

Several years later were published by Conti, et al. [14] in Diabetes a paper where glucose production was investigated in isolated hepatocytes and during pancreatic clamps in healthy rats treated with the ureidic compound. In the same article was also investigated glucose metabolism and insulin sensitivity on C57BL/6j, db/db, high-fat fed mice, and rats after chronic treatments. The conclusions were that the ureidic compound, in vitro and in animal models, reduces gluconeogenesis and improves glucose homeostasis, refreshing the interest in selective and reversible L-CPT1 inhibition as a potential antihyperglycemic approach.

After exposure of these encouraging results and by-passed the obstacle of irreversibility and selective inhibition of CPT1 alone, the question is: why no pharmaceutical company has invested resources in this direction to make it a new antidiabetic drug? Perhaps, because of side effects this type of pharmacological approach on diabetes control could result blocking selectively liver CPT1 isoform; in fact, this isoform is also implicated in CNS control of food intake [15]. In addition, some negative aspects were already highlighted in previous studies such as steatosis [16] and apoptosis [17,18]; the latter aspect as to generate a new stream of research to anticancerogenic action due to CPT1 inhibition [19,20]. Moreover, other dangerous negative aspects of CPT blocking such as cardiac mitochondrial toxicity [21], cardiac hypertrophy [22,23] and mortality for prolonged inhibition [24] emerged in other studies; consider that diabetes is a chronic disease and as such should be treated, the continued blockade of the CPT may be contraindicated? In contrast, some evidence had emerged from other CPT inhibitors to ameliorate or not effect on cardiac performance as result of inhibition [11,24,25]. In addition, a recent report showed that a long-term decrease in hepatic fatty acid oxidation leads to a beneficial effect in a mouse model of obesity and diabetes [26]. The fact is that clinical studies on CPT inhibitor were discontinued. In conclusion, we can relaunch the Arudini’s provocation by placing the problem: is inhibition or activation preferable? [27,28].

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