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Glucose-6-Phosphatase: Novel Therapeutic Approaches for Type 2 Diabetes

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The glucose 6-phosphatase (G6Pase) is an enzyme found in a number of tissues comprising liver, kidney, muscle and also in intestine and pancreatic islets and others [1]. This enzyme plays an important part in starvation period of plasma glucose. In liver, G6Pase is the last step of the glycogenolysis that leads to the glucose release under the glucagon stimulation in order to adjust the glycemia [2]. Unlike the most of phosphatase known, G6Pase is a membrane multi-component protein complex of the reticulum endoplamic with its catalytic site in regard of the lumen. The model of G6Pase system has been described by Van Schaftingen and Gerin [3] with the catalytic domain, the T1 translocase for glucose 6-phosphate (G6P) uptake, a T2 Pi (PPi) transporter and a T3 glucose transporter. Molecular studies have lead to identify a gene family encoding the G6Pase catalytic subunit including G6PC, G6PC2 and G6PC3 [1]. G6PC gene is expressed mainly in the liver and kidney, but also in the intestine and pancreatic islets. G6PC2 gene initially called the islet-specific G6PC-related protein (IGRP) produces an isoform specifically in the pancreatic tissue [4,5] that suggested a potential role of the G6Pase in the regulation of islet insulin secretion. The G6PC3 also called the ubiquitously expressed G6PC-related protein (UGRP) was expressed in every tissue analyzed [1]. Martin et al. [5] have showed that rat islet G6PC2 is a no functional pseudogene that which inacordance consistent with a G6Pase function in β cell specific regulation. But, nonetheless Schmoll et al. [6] have successfully amplified a G6PC-like cDNA that demonstrated the expression of a G6PC gene equivalent in insulinoma cell line (INS1). We can so consider that the G6PC2 defective gene in rat has been compensate by a G6PC-like gene expression. These authors have showed that the G6PC gene expression is up-regulated by high glucose level suggesting a protection against high glucose load. Several studies have shown that the G6Pase undergoes post-translational regulation. In the same time, a G6PC T1 translocase has been identified [7]. Arion et al. [8] showed the presence of two independent binding sites on the G6P transporter T1 that are involved in the hydrolysis of glucose 6-phosphate showing evidence for the regulator role of T1 in G6Pase activity. The work of Clottes and Burchell [9] confirmed this dependance of the G6Pase activity at the translocase T1. The authors have used a specific sulfhydryl reagent on the three thiol groups on T1 translocase of liver G6Pase system showing a modulation of the translocase activity. These authors have proposed a T1 translocase regulation although a conformational model. Moreover, it's now clearly established that chlorogenic acid, a caffeoylquinic acid derivative interacts with the T1 translocase preventing thereby the entry of G6P substrate [10] leading to reduce the G6Pase activity. Chlorogenic acid effect has been correlated with a decrease of glucose release by the hepatic tissue.

Studies reported that G6Pase activity was been several fold higher in islets from hyperglycemic or diabetic rats compared to normal animals [11]. In ob/ob mice an increase of the G6Pase activity specially in pancreatic β cells participates to hyperglycemia by a reduction of insulin secretion [12]. In islets isolated from partially pancreatectomized rats, glucose-induced insulin secretion is impaired and G6PC expression is elevated compared to controls [13]. Transfected MIN 6 cells with a G6PC genetic construct induce a high reduction of Glucokinase/G6Pase ratio and are so quickly followed by reduction of insulin secretion [14]. This transfected-cells experiment approach has confirmed that a G6Pase modulation activity is correlated to a modulation of insulin secretion like that is early proposed by Malaisse [15].

We have previously shown that chlorogenic acid and a root chicoric acid rich extract are able to stimulate insulin secretion with the similar efficiency, but only chicoric acid rich extract acts with a glucose dependence effect [16]. Recently, we have showed that the chicoric acid rich has no effect on the microsomal hepatic G6Pase fraction [17]. More recently, we have evaluated the G6Pase on pancreatic (INS1) microsomal fractions using the same protocol that in Azay-Milhau et al. [17]. We have observed a clear decrease of G6Pase activity on β cells microsomal fraction in the presence of chlorogenic acid (-56%, $P<0.01$) and of chicoric acid extract (-20%, $P<0.05$) at 50 $\mu g.mL^{-1}$ versus controls (4.42 ± 0.44 Pi [$pmole.hour^{-1}$ for 2µg of proteins]). Also, we observed a clear decrease of G6Pase activity related to an increase of the glucose concentration in the medium (personal communication). The inhibitor effect of the two caffeoyl acid derivatives seems however implicate different signaling pathways since chicoric acid extract act only in β cells. Interestingly, G6Pase activity of islet cells presents some differences with those of hepatocytes. The two types of cells display distinct K_m, pH dependence, and inhibitor profiles of their G6Pase activities [18,19]. One important data might be to know the transport mechanism required for the action of chlorogenic acid or chicoric acid extract.

In another hand, Asteraceaes (Artichoke, Chicory, Burdock, Purple Coneflower, Dandelion) known for their antidiabetic virtues [20] are characterized by their rich polyphenolic contents including a large number of hydroxycinnamic acid derivatives as chlorogenic acid, caffeic acid, ferulic acid, chicoric acid known for their antihyperglycemic effects [16,17]. So the use of chlorogenic acid or chicoric acid extract included in food could be attractive for a preventive antidiabetic treatment. The compounds can act by three independently effects; the reduction of the discharge of glucose by liver, the stimulation of insulin secretion by β cells and the uptake of glucose by the muscle.

So future researches upon pancreatic β cells G6Pase activity in its implication in type 2 diabetes genesis might to be considered for importance in view to obtain a new target for treatments.

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