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Diabetes and the role of isoprenoid biosynthesis

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The elegant studies conducted in vitro by Chamberlain [1] demonstrate convincingly that the HMG-CoA reductase inhibitor lovastatin, a widely clinically used cholesterol-reducing drug distributed as Mevacor, also inhibits physiological insulin-stimulated glucose transport. The author postulates that the mechanism of this effect is via the inhibition of isoprenoid biosynthesis, another intermediate product of the cholesterol complex pathway. As expected, this effect was reversed by the isoprenoid (and cholesterol) precursor mevalonate.

The offered concept that defects in isoprenoid metabolism can lead to cellular insulin resistance is a major step forward, with decisive theoretical and clinical consequences. The author speculates further that the possible intimate mechanism involves the inhibition of the protein prenylation by farnesol and geranylgeraniol – also intermediates of cholesterol biosynthesis. Yet, another reasonable mechanism, not entertained by Dr. Chamberlain, is the involvement of one of the end-products of the cholesterol biosynthetic pathway – coenzyme Q.

It is now well established that the cholesterol-reducing drugs known as statins also restrain the biosynthesis of coenzyme Q (coenzyme Q_{10} in humans or ubiquinone), with reported clinical consequences (reviewed in [2,3]). Coenzyme Q is a vitamin-like, fat-soluble nutrient (a quinone) and functions as a vital component of the mitochondrial energy electron transduction chain and ATP production, as a powerful antioxidant, and as a membrane stabilizer. The cardioprotective, cytoprotective, and neuroprotective clinical potential of coenzyme Q, and its involvement in the so-called diseases of bioenergetics, is subject of many publications and international symposia.

A thesis has been advanced that at least some of the statins' recognized side effects result from the coenzyme Q_{10} endogenous biosynthesis suppression, culminating in the development of a coenzyme Q_{10} deficiency.

An early study indicates [4] that the coenzyme Q_{10} blood level in diabetics is significantly lower and furthermore, four antidiabetic drugs tested also lowered this coenzyme Q_{10} level. A farsighted interpretation of this observation by the authors is that coenzyme Q_{10} deficiency in the pancreas could impair bioenergetics, the generation of ATP, and the biosynthesis of insulin. Similar conclusions were reached much later by McCarty [5]. In 2001, Langin published a study substantiating the link between diabetes, insulin secretion, and the pancreatic β-cell mitochondrial function. According to the study, mitochondrial ATP increase inhibits ATP-sensitive potassium channels, which in turn stimulates insulin secretion. In the process of generating ATP, control of the coupling between oxygen consumption and ATP synthesis is essential, since it modulates ATP levels [6].

Several lines of evidence strongly suggest that insulin resistance and diabetes type I and II are associated with increased production of reactive oxygen species, oxidative stress, and reduced antioxidant defences (reviewed in [7]). It has also been demonstrated that acute hyperglycemia stimulates the production of free radicals [7]. For this and other reasons, the European Association for the Study of Diabetes organized in 1998 an 'Expert Session' on oxidative stress [8]. Furthermore, there are encouraging data pointing to a favorable effect in diabetic patients treated with antioxidants – vitamins E and C [7,9] and more recently with α-lipoic acid [9,10].

Studies demonstrating clinical improvement in diabetics treated with coenzyme Q_{10} were initiated as early as 1966. The results of five early clinical trials, using very low coenzyme Q_{10} doses, were reviewed by Yamamura [11]. In a more recent study [12], a randomized double-blind, placebo-controlled trial of 62 patients treated with the equivalent of 300 mg/day coenzyme Q_{10} showed a significant reduction of their fasting and postprandial blood glucose and their fasting insulin level, indicating an improved hyperglycemia and insulin sensitivity. A further thought-provoking topic is a review by Sinatra [13], which includes a short chapter on the diabetes–coenzyme Q_{10} relationship.

The basic and clinical details presented, in part, in this short synopsis support strongly the biochemical premise offered by Chamberlain [1], and justify further the organization of larger, state-of-the-art clinical trials evaluating the coenzyme Q_{10} role as an adjunctive treatment for diabetes, alone or in combination with other antioxidants. Equally consequential will be the prospective study of the management of the complications associated with the progression of this debilitating disease, injuring many compartments of the body, most importantly the cardiovascular system.

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