Accumulated End Products Participate in Glucose Intolerance and Insulin Resistance in Uremia

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Dear Sir,

Mark and DeFronzo [1] reviewed 'Glucose and insulin metabolism in uremia' in Nephron, recently. The review of the distinguished contributors presents a clearcut evidence on the mechanism and significance of this alteration. However, one of the mentioned points is to be extended: insulin resistance and glucose intolerance (IR/GI) in uremia, besides common mechanisms with other diseases share a specific feature, i. e., the effect of accumulated end products excreted or eliminated otherwise insufficiently by the kidney. At least 2 end products were defined sufficiently, i.e., hippurate [2] and pseudouridine [3] which accumulate in uremia because of insufficient urinary excretion.

Hippurate inhibits glucose utilization in isolated rat diaphragm (table 1) at concentrations found in uremia, with maximal inhibitory activity 86,6%. Moreover, it inhibits also insulin-stimulated glucose utilization if insulin is administered to rats in vivo 30 min before sacrifice to assure its binding and even partial internalization [4].

Pseudouridine inhibits glucose utilization in isolated rat soleus muscle (intact superficial membrane) also at concentrations found in uremia [5]. It inhibits insulin-stimulated glucose utilization both in the case of insulin addition to incubation medium or administered to rat in vivo. Pseudouridine inhibits also tolbutamide-stimulated glucose utilization by 30%.

However, tolbutamide stimulates glucose utilization independently from insulin receptor by closing the ATP-depend-ent K⁺ channel and by opening a voltage-operated Ca channel and increasing Ca concentration intracellularly. As intracellular Ca concentration is also a link of insulin regula-

tory cascade, it could be hypothesized that modulation of intracellular free Ca concentration in muscle is the site of the inhibition of IR/GI caused by these accumulated end products. In accordance with these results is also the inhibition of glucose utilization by diltiazem and the additive effect of pseudouridine (table 1).

The finding of the hippurate and pseudouridine insulin postreceptor effect is in accordance with the insulin postreceptor inhibition of glucose utilization in patients [6] and the localization of inhibition at the intracellular Ca with the potential significance of PTH and hormones of vitamin D [1].

The accumulated hippurate, pseudouridine and eventually other inhibitors could participate in the late development of IR/GI in most patients with kidney diseases in contrast to early development of IR/GI in other diseases such as hypertension or obesity.

Table 1. The effect of hippurate [4] and pseudouridine [5] on glucose utilization

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