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Short Communication: Defective Insulin Response to Intravenous Glucose in Congenital Lactic Acidosis

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Congenital lactic acidosis has been shown to result from defective pyruvic acid metabolism, namely pyruvate dehydrogenase complex, pyruvate carboxylase, or neoglucogenic enzymes deficiencies. Nevertheless, the underlying defect has not been adequately elucidated in a large number of patients (1). During the investigation of pyruvate metabolism in patients with congenital lactic acidosis, we performed intravenous glucose tolerance tests and observed a defective insulin response.

We investigated chronic lactic acidemia (5 to 10 mM) in four patients who also displayed delayed neurologic development and failure to thrive. There were two control subjects. Ages of the six individuals ranged from 2 months to 1 year. Subjects with lactic acidemia had normal enzymatic activities in broken fibroblasts (*i.e.*, pyruvate dehydrogenase, pyruvate carboxylase, and neoglucogenic enzymes) and normal basal blood glucose levels. Intravenous glucose tolerance tests were performed after a 12-h fast and normalization of the blood pH with sodium bicarbonate. Ten mmoles/kg glucose were injected over a 5-min period and blood samples were obtained over the next 180 min. Glucose and insulin concentrations were determined in each samples. Blood glucose rose to 30 ± 5 mM at 10 or 15 min and returned to normal at 90 min. There was no difference between patients and controls (see Fig. 1) and lactic acidemia was unchanged. In the 4 affected patients, no insulin response was observed (<20 μU/ml) in contrast to controls in whom insulin response parallels the glucose rise. The insulin response to other insulin-releasing substances such as 0.5 g/kg L-arginine IV and 20 mg/kg tolbutamide IV was tested and found to be normal. Therefore, the defective insulin response seems to be specific for glucose.

It is now generally accepted that the glucose metabolism in the pancreatic β cells plays a crucial role in the mechanism which stimulates insulin release (2). More precisely it has been proposed that the metabolism of glucose affects the concentration of pyridine nucleotides which in turn may modulate ionophoretic processus in the β cell (3). Therefore, it is tempting to speculate that a decreased pyruvate flux through pyruvate dehydrogenase as observed in congenital lactic acidosis might be responsible for the defective insulin response to glucose stimulation. Indeed the insulin response was normal when stimulated by L-arginine and tolbutamide. The striking point in our observation is the absence of diabetes in the affected patients. Blood glucose returned to basal level at the same time in patients and controls during the glucose tolerance tests. There was probably enough circulating insulin to stimulate the cellular glucose uptake. Nevertheless the regulation of the pyruvate dehydrogenase complex is insulin dependent (4) and a decreased insulin response to glucose may favor an accumulation of lactate in these patients. Unfortunately we do not know the underlying disorder in our patients and hence can not definitively conclude whether or not the primary defect results from defective pyruvate metabolism or a defective insulin response to glucose. This emphasizes the necessity to perform intravenous glucose tolerance test in all patients with congenital lactic acidosis.

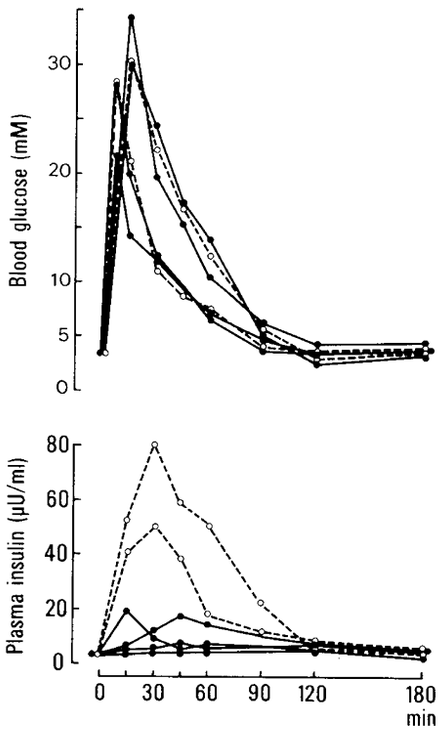

Fig. 1. Insulin response to intravenous glucose tolerance test (10 mmoles/kg in four patients with congenital lactic acidosis (●——●) and two controls (O---O).

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