Abnormal Leucine Induced Insulin Secretion in Chronic Renal Failure

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Chronic renal failure(CRF) is associated with a sundry of abnormalities in pancreatic islets including a rise in their cytosolic calcium[Ca^{2+}]i, reduced ATP content and impaired glucose induced insulin secretion. The latter is also stimulated by aminoacids(such as leucine), and the cellular processes involved in leucine induced insulin secretion are different from those responsible for glucose induced insulin release.

The mechanisms through which leucine induces insulin secretion are complex and at least two mitochondrial processes are involved. The first entails the deamination of leucine resulting into NH_3 and α-ketoisocaproic acid. The latter compound enters the citric acid cycle and its metabolism by the branched chain ketoacid dehydrogenase(BCKDH) leads to production of ATP. The rise in ATP closes the ATP dependent K^+-channel of the islet cell membrane resulting in cell depolarization with subsequent activation of voltage dependent calcium channels. As a consequence, calcium enters the islets causing a rise in [Ca^{2+}]i that triggers cellular events which lead to insulin secretion. Indeed α-ketoisocaproic acid depolarizes the beta cell membrane and induces insulin secretion in the absence of glucose or leucine. Second mitochondrial pathway underlying leucine induced insulin secretion involves the activation of mitochondrial glutamate dehydrogenase(GLDH) which deaminate glutamate generating NH^+ and α-ketoglutarate, the metabolism of which triggers insulin secretion. This pathway dose not require the metabolism of leucine since the nonmetabolizable analogue of leucine, 2-aminobicylo(2-2-1) haptene(BCH), allosterically activates GLDH and subsequently triggers insulin secretion. The present study examined whether leucine induced insulin secretion is also impaired in CRF and investigated the cellular derangements for such a potential abnormality.

The results showed that leucine induced insulin secretion is markedly reduced by islets from CRF rats, and this defect was prevented by parathyroidectomy(PTX) of the CRF rats or by their treatment with verapamil, an agent that blocks the action of PTH on the pancreatic islets. Both leucine uptake and α-ketoisocaproic acid induced insulin secretion by CRF rats are normal, but the activation of GLDH by leucine or by BCH and the utilization of α-ketoglutarate are impaired and the Vmax of glutaminase is reduced in the islets from CRF rats. All the derangements are corrected by PTX of the CRF rats or by their treatment with verapamil.

The data demonstrate that

1) CRF is associated with impaired leucine induced insulin secretion,

2) this defect is due to the state of secondary hyperparathyroidism of CRF, and

3) the cellular derangements responsible for this defect involve abnormalities in the leucine-GDLH-α-ketoglutarate-glutaminase pathway that is involved in leucine induced insulin secretion.