

Incretin hormones and beta-cell function in chronic pancreatitis

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ABSTRACT

Type 2 diabetes has been shown to be characterized by an almost abolished incretin effect. The incretin effect refers to the phenomenon of oral glucose eliciting a higher insulin response than intravenous glucose at identical plasma glucose profiles. It is conveyed by the two insulinotropic incretin hormones: glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). GLP-1 and GIP are secreted from the small intestines in response to ingestion of nutrients. The incretin defect of type 2 diabetes has been characterized by a virtually lost insulinotropic effect of GIP. It is unknown whether the incretin defect is a primary event leading to type 2 diabetes or arises as a consequence of the diabetic state. To investigate this we studied patients with chronic pancreatitis. Over time, chronic pancreatitis leads to secondary diabetes. If patients with chronic pancreatitis and secondary DM exhibit the characteristic type 2 diabetic incretin deficiencies and patients with chronic pancreatitis and normal glucose tolerance are normal in that regard, it is more likely that these deficiencies are consequences of the diabetic state rather than primary events leading to type 2 diabetes. On the other hand, if incretin physiology is preserved independently of the endocrine status of patients with chronic pancreatitis, the incretin defect could represent a primary pathogenetic defect. Three protocols have been employed to investigate this. In a study investigating postprandial incretin responses in eight patients with chronic pancreatitis and exocrine pancreatic insufficiency, with and without pancreatic enzyme supplementation, we observed preserved incretin responses as compared to matched healthy subjects; and, further, that pancreatic enzyme supplementation increased postprandial incretin responses in these patients. This suggests not only that the secretion of incretin hormones is regulated by the mere presence of nutrients in the small intestine, but also that the assimilation of such nutrients is involved, as well. Furthermore, we gauged the incretin effect in eight patients with chronic pancreatitis and normal glucose tolerance and in eight patients with chronic pancreatitis and secondary diabetes. Eight healthy subjects and eight patients with type 2 diabetes were studied for comparison. The incretin effect was shown to be preserved in normal glucose tolerant patients with chronic pancreatitis, whereas it was strongly reduced in patients with chronic pancreatitis and secondary diabetes, suggesting the incretin defect to be a consequence of the diabetic state. Lastly, we investigated the insulinotropic effect of the incretin hormones in eight patients with chronic pancreatitis and normal glucose tolerance and in eight patients with secondary diabetes, and observed that patients with chronic pancreatitis and secondary diabetes exhibit an impaired insulinotropic effect of GIP, and that this most likely occurs as a consequence of the diabetic state. In conclusion, we suggest

that: 1) the postprandial secretion of incretin hormones is preserved among patients with chronic pancreatitis, 2) assimilation of nutrients stimulates secretion of GIP and GLP-1, and 3) the characteristic incretin deficiencies of type 2 diabetes most likely are consequences of a deteriorating glucose homeostasis, rather than primary events leading to type 2 diabetes.