Abstract: 33S

The role of a bile acid-GLP-1 axis in the regulation of glucose metabolism

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Background: Bile acids are recognised to play an important role in glucose homeostasis. We have reported that small intestinal administration of taurocholic acid (TCA) reduces the glycaemic response to intrajejunal (IJ) glucose infusion in healthy humans markedly, associated with stimulation of plasma glucagon-like peptide-1 (GLP-1). We have now evaluated the effect of TCA, with or without the GLP-1 receptor antagonist, exendin(9-39), on the glycaemic response to an IJ glucose infusion in patients with type 2 diabetes (T2DM).

Materials and methods: 10 T2DM patients, managed by diet or metformin alone, were each studied on four study days, separated by ≥7 days, in a double-blind, randomised fashion. On each day, an IJ catheter was positioned and a balloon inflated 30 cm beyond the pylorus to allow proximal aspiration of endogenous bile. An intravenous (IV) infusion of exendin(9-39) (600 pmol/kg/min) or 0.9% saline was commenced and maintained during t = -60-120 min. TCA (2g in 0.9% saline), or saline, was given via IJ infusion during t = -30-0 min, followed by 2 g TCA or saline, together with 60 g glucose, during t = 0-120 min. Blood glucose and plasma insulin, C-peptide and glucagon were measured at regular intervals. The insulin secretion rate (ISR)/glucose ratio was also calculated.

Results: TCA reduced blood glucose ($P = 0.022$), and increased plasma insulin ($P = 0.007$) and the ISR/glucose ratio ($P = 0.022$), without affecting plasma glucagon. In contrast, exendin(9-39) was associated with higher blood glucose ($P = 0.003$) and plasma glucagon ($P = 0.011$), and reductions in plasma insulin ($P = 0.008$) and the ISR/glucose ratio ($P < 0.001$). In the absence of exendin(9-39), blood glucose was lower ($P = 0.010$), and plasma insulin ($P = 0.025$) and the ISR/glucose ratio ($P = 0.039$) were greater, with TCA vs. control, without any difference in plasma glucagon. In the presence of exendin(9-39), plasma insulin was greater with TCA vs. control ($P = 0.020$), without any difference in blood glucose, the ISR/glucose ratio, or plasma glucagon.

Conclusion: In T2DM, small intestinal administration of TCA reduces the glycaemic response to IJ glucose, associated with an increase in insulin secretion, and these effects are attenuated by exendin(9-39). These observations support the concept of a “bile acid-GLP-1” axis in the regulation of postprandial glycaemia in T2DM.