Differential regional metabolism of glucagon in anesthetized pigs

Glucagon metabolism under basal (endogenous) conditions and during intravenous glucagon infusion was studied in anesthetized pigs by use of midregion (M), COOH-terminal (C), and NH2-terminal (N)-RIAs. Arteriovenous concentration differences revealed a negative extraction of endogenous glucagon immunoreactivity across the portal bed (-35.4 +/- 11.0, -40.3 +/- 9.6, -35.6 +/- 16.9%, M-, C-, N-RIA, respectively), reflecting net secretion of pancreatic glucagon and intestinal glicentin and oxyntomodulin, but under exogenous conditions, a net extraction occurred (11.6 +/- 3.6 and 18.6 +/- 5.7%, C- and N-RIA, respectively). Hindlimb extraction of endogenous (17.4 +/- 3.7%, C-RIA) and exogenous (29.1 +/- 4.8 and 19.8 +/- 5.1%, C- and M-RIA) glucagon was detected, indicating M and C cleavage of the molecule. Renal extraction of glucagon was detected by all assays under endogenous (19.4 +/- 6.7, 33.9 +/- 7.1, 29.5 +/- 6.7%, M-, C-, N-RIA) and exogenous conditions (46.9 +/- 4.8, 46.4 +/- 6.0, 47.0 +/- 7.7%; M-, C-, N-RIA), indicating substantial elimination of the peptide. Hepatic glucagon extraction was undetectable under basal conditions and detected only by M-RIA (10.0 +/- 3.8%) during glucagon infusion, indicating limited midregional cleavage of the molecule. The plasma half-life determined by C- and N-RIAs (2.7 +/- 0.2 and 2.3 +/- 0.2 min) were similar, but both were shorter than when determined by M-RIA (3.2 +/- 0.2 min, P <0.02). Metabolic clearance rates were similar regardless of assay (14.4 +/- 1.1, 13.6 +/- 1.7, 17.0 +/- 1.7 ml.kg(-1).min(-1), M-, C-, N-RIA). Porcine plasma degraded glucagon, but this was not significantly affected by the dipeptidyl peptidase IV (DPP IV) inhibitor valine-pyrrolidide, and in anesthetized pigs, glucagon's metabolic stability was unchanged by DPP IV inhibition. We conclude that tissue-specific metabolism of glucagon occurs, with the kidney being the main site of removal and the liver playing little, if any, role. Furthermore, valine-pyrrolidide has no effect on glucagon stability, suggesting that DPP IV is unimportant in glucagon metabolism in vivo, in contrast to its significant role in the metabolism of the other proglucagon-derived peptides and glucose-dependent insulinotropic polypeptide.