Peripheral Effects of Ex-4 and GLP-1 on Anorexia and Weight Loss

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Significance and Background: Glucagon-like-peptide-1 (GLP-1) is secreted from enteroendocrine L-cells after meals and enhances glucose-stimulated insulin secretion from pancreatic beta-cells. GLP-1 acts through a specific GLP-1 receptor (GLP-1r) that is expressed by cells of the pancreatic islet, the GI tract, and the brain. When administered directly to the CNS GLP-1 reduces food intake. While the properties of GLP-1 raise the possibility that it would make a good diabetes drug, it is rapidly inactivated in the circulation by the enzyme DPP-IV making its use problematic. Two strategies have been taken to use GLP-1r signaling in pharmacology. Exendin-4 (Ex-4) is an agonist of the GLP-1 receptor that is not susceptible to DPP-IV, and improves glucose control and causes weight loss in diabetic patients. DPP-IV inhibitors block the metabolism of endogenous GLP-1 and improve glucose control similarly to Ex-4, but do not cause weight loss. We sought to determine why drugs that act through the GLP-1r system differ in their relative potencies for glucose control and anorexia. We hypothesized that this difference was because subjects treated with Ex-4 have higher circulating GLP-1r agonist activity than subjects treated with a DPP-IV inhibitor. To test this question we gave GLP-1 with the DPP-IV inhibitor vildagliptin (Vi) and compared the effects on food intake to animals treated with Ex-4.
Methods: 350-400 g male Sprague-Dawley rats were given intraperitoneal (IP) GLP-1, Ex-4, Vi, GLP-1 + Vi or Ex-4 + Vi thirty min prior to the dark cycle and food intake was measured at 0.5, 1, 2, 4, 6 and 24 h. To control for the effect of the IP injection itself and for day-to-day variability another group of rats was injected with saline. In a second study 3 doses of GLP-1 were given with Vi to test their effects on food intake.
Results: Neither GLP-1 nor Vi given 30 minutes before the onset of feeding reduced food intake in our rats. However, co-administration of Vi and GLP-1 suppressed food consumption for up to 4 hours. When combined with Vi, GLP-1 reduced food intake similarly at 10, 100, and 500 μg doses, although the highest does had a longer effect. A 12.7 μg dose of Ex-4 reduced food intake for 24 hours and caused weight loss. Surprisingly addition of Vi to Ex-4 had an additive effect to reduce food intake.
Conclusion: The failure of either GLP-1 or Vi alone to reduce food intake is likely due to insufficient plasma levels of active hormone, since the combination induces anorexia. When protected by Vi even small amounts of GLP-1 reduce food intake, with an apparent threshold effect at a dose of 10 μg. On a molar basis, Ex-4 seem to be more potent and longer lasting in suppressing food intake than GLP-1, and this effect appears to be dose dependent. The distinct pharmacodynamics of GLP-1 and Ex-4, and the additive effect of Ex-4 and Vi raise the possibility that these GLP-1r agonists affect feeding by different mechanisms. Understanding the specific pathways by which Ex-4 and DPP-IV protected GLP-1 act will allow optimal use of GLP-1 based drugs in diabetic patients.