

Validating GLP-1 Agonist/Antagonist System Using Continuous Infusion by Osmotic Pump

Jatin Dhimar, Zhibo An, Eric P. Smith, David A. D'Alessio

Background: Obesity is a growing worldwide epidemic that causes high morbidity and mortality. While lifestyle changes and medical interventions for obesity have been ineffective, bariatric surgery, in particular Roux-en-Y gastric bypass (RYGB) has become an increasingly common treatment. Animals and humans that have RYGB show metabolic improvements independent of weight loss. GLP-1 is an intestinal hormone secreted after meals; its effects include increasing insulin secretion and inducing satiety. Due to the markedly increased post-prandial levels of GLP-1 following RYGB, it has been speculated this may account for some of the benefits of RYGB. However, a causal relationship between higher levels of GLP-1 in RYGB and metabolic improvement has not been established. A strategy for demonstrating a direct role for GLP-1 would be to block its actions with a specific inhibitor, Exendin-9 (Ex-9). My study was designed to establish an effective concentration of Ex-9 that could block GLP-1 activity *in vivo* to preparation for subsequent studies by others on the RYGB rat model. **Methods:** 24 male Long-Evans rats had subcutaneous implantation of osmotic pumps containing either saline, Ex-9 (3 pmol/kg/min), or Ex-9 (30 pmol/kg/min). For the food intake (FI) measurement, rats were IP injected with 3ug/kg of GLP-1 agonist Exendin-4 (Ex-4) or saline. For assessing glucose tolerance, rats were IP injected with an inhibitor of GLP-1 inactivation, Vildagliptin, (Vilda), 10mg/rat, or saline. **Results:** 3ug/kg Ex-4 caused a significant decrease in FI but there was no effect of Ex-9 at either dose. Similarly, though Vilda significantly improved oral glucose tolerance there was no effect of the Ex-9. However, in a final experiment, an acute injection of 100 ug of Ex-9, was able to reduce the effects of simultaneous injection of Vilda. **Conclusions:** Exendin-4, resistant to inactivation and with, therefore, a longer half-life compared to native GLP-1, may not be the best agent to test the biologic activity of Ex-9. When provided at sufficient doses, however, Ex-9 is able to block the actions of endogenous GLP-1 increased by injection of Vilda. Ex-9 concentrations, when administered by constant infusion, appeared not to be high enough to block endogenous GLP-1 actions at the doses applied. Future experiments using increased doses will establish what the effective dose will be for the subsequent RYGB study .