GLP-1 – The New Darling of Diabetes Treatment

Glucagon-like peptide-1 (GLP-1) is an incretin hormone that regulates postprandial insulin secretion. The incretin effect is believed to be critical for maintenance of normal plasma glucose and glucose tolerance (*Diab* 1995). Experiments using antagonists of the GLP-1 receptor show that GLP-1 is responsible for a substantial part of the insulin response to oral glucose (*Diab* 1995) (*Diab* 1994).

GLP-1's physiological effects, as explained by Jens Juul Holst, MD, PhD, University of Copenhagen, Denmark, are that it causes glucose dependent insulin secretion, inhibits glucagon secretion, delays gastric emptying and increases satiety GLP-1 may also cause beta cell growth (shown *in vitro* and in animal studies), have neuroprotective effects, and have favorable cardio-vascular effects, he said, but these are not known yet for sure (Vilsbøll et al, *Regulatory Peptides* 2003).

Only 10 to 15 percent of secreted GLP-1 reaches the pancreas intact, but GLP-1 action may involve the central nervous system as well. GLP-1 secretion must be measured as the sum of active GLP-1 and its metabolite GLP-1 (9-36) amica. A study cited in *Nature* magazine (1996) stated that ICV administration of GLP-1 inhibits food intake in rats.

Exendin-4: More Than Just a GLP-1 Receptor Agonist?

Exendin-4 (exenatide), taken from the saliva of the Gila monster, is 53 percent homologous with GLP-1 and acts as an agonist at the GLP-1 receptor. It is also insensitive to DPP-4, the enzyme that degrades GLP-1.

"Exendin-4 provides has several mechanisms of action: it causes glucose dependent insulin secretion, suppresses postprandial hyperglucagonemia, delays gastric emptying, contributes to weight loss and may decreases insulin resistance and restore beta cell function," explained Dr. Vahl.

Dr. Vahl also pointed out that other studies have shown that continuous subcutaneous infusion of GLP-1 for 6 weeks improves fasting and postprandial hyperglycemia (PPHG) in Type 2 diabetes, reduces HbA1C level by 1.3%, and reduces body weight. Kendall et al (ADA 2005) noted progressive body weight reduction in exenatide-treated patients, and DeFronzo (*Diab Care* 2005) and

Buse (*Diab Care* 2005) also found that Exendin-4 decreased body weight and restored first phase insulin secretion (*JCEM* 2005).

Henry (ADA 2006) and his colleagues studied change in body weight for a 2-year completer population in an open-label uncontrolled study. Over 2 years, weight reduction from baseline was -4.7±0.3 kg and treatment with exendin-4 led to sustained improvement in glycemic control. Linnebjerg (ADA 2006) showed that exenatide slowed gastric emptying in a dose dependent fashion.

Another exciting development is exenatide's long-acting release (LAR) technology, which utilizes biodegradable polymeric microspheres for extended drug release. Liraglutide is the long action form of exenatide. Exenatide's plasma concentration is detectable weeks to months after a single dose of liraglutide, according to Dr. Nauck. Liraglutide has been shown to reduce systemic blood pressure (Vilsboll ADA 2006), triglycerides, PAI-1 and BNP concentrations in patients with Type 2 diabetes, though these observed effects need to be explored further. It also seems to offer weight reduction comparable to sibutramine and rimonabant.

New Directions in Incretin Therapy: DPP IV inhibitors

Additional therapies on the horizon that utilize the incretin system include DPP-4 inhibitors. These are oral medications that block DPP IV, the enzyme that degrades GLP-1. Their mechanism of action is through GLP-1 receptors, possibly GIP receptors, and other receptors as well. Dr. Nauck summarized the potentials of vildagliptin and sitagliptin, two DPP IV inhibitors under active investigation.

Vildagliptin may suppress endogenous glucose production. Dr. Nauck pointed out that vildagliptin also contributes to restoration of the acute phase insulin response, has been associated with a lowering of blood pressure, and reduces postprandial hypertriglyceridemia. It may be used as adjuvant therapy in patients who use insulin. Sitagliptin may be used in patients with renal insufficiency, but it has been found to have pharmacokinetic interactions with glyburide and rosiglitazone, he noted.

Incretin mimetics cause a - 3 to 5 kg weight change depending on dose and duration of action while DPP-4 inhibitors have been associated with less dramatic weight loss. Studies have shown that DPP IV inhibitors are associated with less nausea and hypoglycemia compared to incretin mimetics.

The addition of these exciting new pharmacological agents will enhance our ability to treat and hopefully one day to conquer diabetes worldwide.