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Title: PGx of GLP1R agonists (**HP-00067574**)

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PHARMACOGENOMICS OF GLP1 RECEPTOR AGONISTS (HP-00067574): STUDY PROTOCOL

I. SPECIFIC AIMS AND OBJECTIVES

We hypothesize that genetic variants, GCGR and GIPR, are associated with an altered response to exenatide (a rapidly-acting, short-duration GLP1 agonist) and sitagliptin (a DPP4-inhibitor). We will conduct our studies in the Old Order Amish – a population that is well suited for pharmacogenetic studies, as exemplified by a study identifying variability in the CYP2C19 gene as a critical determinant of clopidogrel responsiveness (15). The 10-fold enrichment of the G40S in GCGR among the Amish greatly facilitates studies of the effects of this SNP. Indeed, a 10-fold increase in the minor allele frequency translates into a ~100-fold increase in the prevalence of homozygotes.

Specific Aim #1: To assess the impact of SNPs in GCGR (G40S) and GIPR (E354Q) on the response to exenatide. Just as homozygosity for either of the SNPs was associated with an impaired response to oral glucose, we hypothesize that homozygosity for either SNP will be associated with an impairment in the beta cell's response to the incretin-like action of exenatide. Approach: Research subjects will undergo a randomized crossover study to assess the effect of exenatide upon insulin secretion. Subjects will be treated with either saline or exenatide (5 mcg, s.c.), prior to undergoing a frequently sampled intravenous glucose tolerance test to assess the pharmacodynamic impact of exenatide upon glucose-stimulated insulin secretion. Homozygotes for the common "wild type" alleles of both GCGR and GIPR will be compared to two study groups: homozygotes for two variant alleles (S40-GCGR homozygotes or Q354-GIPR homozygotes).

Specific Aim #2: To assess the impact of SNPs in GCGR (G40S) and GIPR (E354Q) on the response to sitagliptin. We hypothesize that homozygosity for either SNP will be associated with an impairment in the beta cell's response to the decreased degradation of incretins. Approach: Research subjects will undergo a crossover study to assess the effect of sitagliptin upon glucose-stimulated insulin secretion. Subjects will be treated with either placebo or sitagliptin (100 mg orally), prior to undergoing an oral glucose tolerance test to assess the pharmacodynamic impact of sitagliptin upon glucose-stimulated insulin secretion. Homozygotes for the common "wild type" alleles of both GCGR and GIPR will be compared to two study groups: homozygotes for two variant alleles (S40-GCGR homozygotes or Q354-GIPR homozygotes).

Specific Aim #3: To assess the effect of the two SNPs (G40S in GCGR and E354Q in GIPR) on oral glucose tolerance tests. Our preliminary data suggesting an association of the two SNPs with delayed insulin secretion in an OGTT is based on a small number of homozygous research subjects. Accordingly, we propose to conduct a replication study to confirm whether this is a reproducible finding. In addition, we will measure hormone levels (glucagon, GIP, GLP1) to investigate mechanisms to compensate for the loss-of-function variants in cognate receptors for glucagon and GIP (GCGR and GIPR).

II. RESEARCH DESIGN: OVERVIEW

Eighty non-diabetic subjects [25 homozygous for p.G40S (GCGR), 25 homozygous for p.E354Q(GIPR) and 30 age/sex matched controls] will be enrolled. Following screening and

baseline blood collection, participants will receive two 3 hour intravenous glucose tolerance tests (IVGTT) separated by a 5 day to 4 week wash-out period. Before each IVGTT, a subcutaneous injection of either 5 micrograms of exenatide or placebo (saline) will be administered. The participant will receive both in a random crossover fashion. After a 1-4 week washout, the participant will return for two 3 hour oral glucose tolerance tests separated by 1-4 weeks, measuring glucose and insulin levels. Before each OGTT sitagliptin (100 mg) or placebo will be administered. The participant will receive both in a random crossover fashion.

III. **RESEARCH DESIGN: OVERVIEW**

Glucagon-like peptide 1 (GLP1) analogs and dipeptidyl peptidase-4 (DPP4) inhibitors are an important classes of anti-diabetic drugs, which combine substantial glucose-lowering activity with clinically meaningful weight loss (in the case of GLP1 analogs). In recently published Guidelines (1,2), the ADA and EASD reviewed 12 classes of drugs for treatment of type 2 diabetes, and advocated “a patient-centered approach.” However, there is a shortage of scientific data to guide the selection of the best drug for each individual patient. We propose to address a portion of this knowledge gap by conducting a pharmacogenetic study to investigate contributions of genetic variation in determining an individual patient’s response to GLP1 analogs and DPP4 inhibitors. In the present application, we propose studies of the effects of specific genetic variants in two candidate genes associated with abnormalities in beta cell function: GIPR and GCGR.

IV. LITERATURE REVIEW

GLP1 is a member of the secretin family of peptides, a family that also includes glucagon and gastric inhibitory peptide (GIP). GLP1, GIP, and glucagon have complex physiological interactions, which contribute importantly to metabolic regulation. Whereas secretion of GLP1 and GIP is promoted by oral glucose (3), glucagon secretion is stimulated by hypoglycemia. Both GLP1 and GIP function as incretins, thereby potentiating the effect of glucose to promote insulin secretion by pancreatic beta cells (3). While glucagon also promotes insulin secretion (4), glucagon is best known for its functions as a counter-regulatory hormone that opposes many of the actions of insulin (5,6). GLP1 decreases plasma levels of glucagon by inhibiting glucagon secretion (3). Recent work has explored pharmacodynamic interactions among the GLP1, GIP, and glucagon agonist mechanisms by investigating the pharmacology of novel peptides possessing dual agonist (GLP1 plus either GIP or glucagon) or triple agonist activities (GLP1 + GIP + glucagon) (7-9). These unimolecular dual and triple agonists have superior metabolic activity to improve glycemic control, promote weight loss, and reverse hepatic steatosis. These observations raise the possibility that the actions of endogenous GIP and glucagon could affect the response to exogenously administered GLP1 analogs (e.g., exenatide) or DPP4 inhibitors (e.g. sitagliptin).

Functionally significant, nonsynonymous SNPs have previously been identified in GCGR and GIPR, the genes encoding receptors for glucagon and GIP, respectively. The G40S substitution in GCGR (rs1801483) decreases the affinity of glucagon binding (10,11), thereby causing glucagon resistance (12). The E354Q substitution in GIPR (rs1800437) enhances the receptor’s sensitivity to agonist-induced desensitization (13), which could lead to GIP resistance in vivo. Both SNPs have minor allele frequencies of 0.12 in the Old Order Amish population. The G40S SNP in GCGR is ~10-fold enriched relative to the general European-American population whereas E354Q in GIPR is ~2-fold under-represented relative to the general European-

American population. We have obtained preliminary data from the Amish Family Diabetes Study (14) demonstrating that homozygosity for either SNP is associated with impaired insulin secretion in an oral glucose tolerance test – suggesting that these genetic variants compromise beta cell function. Please refer to the following sections of the American Diabetes Association Grant Application and the Diabetes Research Center Pilot & Feasibility grant application:

- Specific Aims
- Section A. Significance
- Section B. Innovation
- Research Approach: Section 1. Scientific Rationale and Background

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V. STUDY PROCEDURES

Recruitment and Screening Visit:
As part of the consent process for Amish Research Clinic studies, participants are asked if we may re-contact them for future studies. Participants who have agreed to re-contact and who have genetic information available from past studies will be asked to participate, based on genotype. Potential participants will be visited in their homes by a field team consisting of a registered nurse and an Amish liaison. This mechanism is culturally appropriate since the Amish do not have phones in their homes and prefer face-to-face contact to letters. Subjects will be asked if they are interested in hearing about another research study. If the subject agrees, the study will be explained and eligibility criteria will be reviewed. Informed consent and HIPAA authorization will be obtained. Following informed consent, vital signs, height, weight, medical and family history will be obtained. Approximately 15 mL (3 teaspoons) of blood will be drawn for CBC, HbA1c, comprehensive metabolic panel, and thyroid function test (TSH) to evaluate eligibility.

Female research participants will be informed that they may not participate in this study if they are pregnant. They will be informed that the risks of exenatide and sitagliptin to a pregnant woman and fetus are unknown. All female subjects will have an assessment of child-bearing potential. Pregnancy status will be determined by self-report at the screening visit. A urine pregnancy test will be performed at the clinic visit prior to drug administration, or within 1 week prior, on women who are not either surgically sterile via tubal ligation, bilateral oophorectomy or hysterectomy or post-menopausal for ≥1 year.

Following review of screening information and lab results, eligibility will be confirmed and the Eligibility Checklist signed by the PI or designated co-investigators. Eligible participants will complete studies during the course of four visits to the Amish Research Clinic. Visits will be

separated by a 5 day to 4 week washout period. FSIVGTT (Frequently sampled intravenous glucose tolerance test) visits will be consecutive and OGTT (Oral glucose tolerance test) visits will be consecutive, but either IVGTTs or OGTTs can occur first. If subjects would like participate in the study, but are unable to accommodate all four visits, they will have the option to do either both FSIVGTT visits or both OGTT visits. (Since the FSIVGTT and OGTT visits are independent of each other, integrity of results will not be altered if subjects only perform one and not the other)
At the first visit only, fasting blood tests will be obtained to assess the lipid profile (LDL, HDL, and triglycerides), DNA, and for plasma and serum banking. Approximately 25 ml (5 tsp.) will be drawn in addition to the blood drawn for the glucose tolerance test at this visit.

FSIVGTT #1 - Research subjects will be transported to the Amish Research clinic in the fasting state (minimum of 8 hour, maximum of 24 hour fast) where height, weight, waist and hip measurements, and vital signs will be measured. Women of child-bearing potential will undergo a urine pregnancy test. An FSIVGTT will be conducted as follows: IV (intravenous) access will be established in both arms of the research subjects, one for glucose infusion and the other for frequent blood sampling. NSS (normal saline solution) will be used to maintain patency of IV. The participants will be randomized to receive a subcutaneous (s.c.) injection of either saline or exenatide (5 mcg) 15 min prior to administration of IV glucose. Intravenous glucose (0.3 g/kg) will be infused over 2 min at time=0, and 31 blood samples will be obtained between -15 and +180 minutes. Approximately 120 ml (24 tsp.) of blood will be drawn.

FSIVGTT #2 - The FSIVGTT will be conducted exactly as during the previous clinic visit. Research subjects will be “crossed over” to receive a s.c. injection of whichever agent they did not receive during the first clinic visit (i.e., saline or 5 mcg exenatide).

OGTT #1 - Research subjects will be instructed to take a single dose of placebo at home at a specified time prior to being transported to the Amish Research clinic in the fasting state (minimum of 8 hour, maximum of 24 hour fast). At the clinic, height, weight, waist and hip measurements, and vital signs will be measured. A single venous access site will be used to collect blood samples. NSS may be infused KVO to maintain patency. The OGTT will begin 2 hours after the placebo was taken. Plasma levels of glucose and insulin will be measured every 30 minutes between 0-180 minutes after oral administration of 75 grams of glucose. In addition, plasma levels of glucagon, GIP, and total GLP1 will be measured at 0, 30, and 60 minutes. Approximately 80 ml (16 tsp.) of blood will be drawn.

OGTT #2 - The OGTT will be conducted exactly as during the previous clinic visit except research subjects will take sitagliptin 100 mg by mouth 2 hours prior to the OGTT. An additional blood sample will be drawn for storage.

Notification of results: Screening lab and lipid results will be reviewed with participants by study team professional at one of the clinic visits. A copy of lab results will be provided to the participants.

VI. SAMPLE SIZE: POWER CALCULATIONS

The two co-primary end-points for the study are both derived from the FSIVGTTs:
• Genotype-dependent effect of exenatide on insulin-AUC. Based on published dose-response

data for liraglutide, insulin-AUC was 13.4 mU/L in placebo-treated individuals. In response to liraglutide (10-12.5 mcg/kg), insulin-AUC increased to approximately 30-36 mU/L with an S.D. of 4-13 mU/L. A sample size of 24 per genotype group would provide 80% power (with alpha=0.05) to detect a decrease of delta insulin-AUC from 20 mU/L (in the control group) to 13.5 mU/L (in homozygotes for a genetic variant) assuming a standard deviation of 8 mU/L (http://www.stat.ubc.ca/~rollin/stats/ssize/n2.html).

• Genotype-dependent effect of exenatide on the disappearance rate for glucose. Based on published dose-response data for liraglutide, Ksubscriptg was 1.00%/min in placebo-treated individuals. In response to liraglutide (10-12.5 mc/kg), Ksubscriptg increased to approximately 1.58-2.39%/min with an S.D. of 0.14-0.23%/min. Thus, delta Ksubscriptg is estimated as ~1.0% (based on an assumption that mean Ksubscriptg would be ~1.0% off-treatment, and would increase to ~2.0% on drug). A sample size of 24 per genotype group would provide 80% power (with alpha=0.05) to detect a decrease of delta Ksubscriptg from 1.0%/min (in the control group) to 0.75%/min (in homozygotes for a genetic variant) assuming a standard deviation of 0.3%/min (http://www.stat.ubc.ca/~rollin/stats/ssize/n2.html).

VII. DATA ANALYSIS

Pre vs. post drug differences between insulin-AUC and disappearance rate for glucose will be calculated for each person and the differences between genotype groups will be tested. Specifically, data will be analyzed using a variance components method that accommodates participant level characteristics (eg. age, sex, renal function) and accounts for relatedness called the Mixed Model Analysis for Pedigrees (http://edn.som.umaryland.edu/mmap/index.php) program.