The Influence of Glucagon-Like-Peptide-1 Receptor Single Nucleotide Polymorphisms on Gastric Emptying Rate in Caucasian Men- A Pilot

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Gastric emptying is the rate-limiting step in the absorption of nutrients in the small intestine. The emptying rate of a glucose solution has been shown to be highly variable between individuals[1]. The gastrointestinal hormone glucagon-like peptide-1 which is prominently secreted following carbohydrate ingestion, has been shown to exert inhibitory effects on gastric emptying rate[2]. Previous work has shown an influence of glucagon-like peptide-1 receptor (GLP-1R) genetic variation on gastric emptying rate in mice[3]. This pilot study investigated the effect of GLP-1R single nucleotide polymorphisms (SNPs) on the rate of gastric emptying in humans.

Forty-eight healthy non-smoking UK Caucasian males aged 18-35 yr (mean ± SD age 23 ± 5 yr, height 178.2 ± 6.9 cm, weight 75.82 ± 11.24 kg, BMI 23.9 ± 3.3, body fat 19.0 ± 6.2%) took part in this investigation. Following an overnight fast, participants completed a single experimental trial involving the ingestion of 595 ml of a 6% glucose solution containing 100 mg ^{13}C sodium acetate. Gastric emptying rate of the solution was measured by ^{13}C breath test whereby breath samples were collected at baseline and 10 min intervals for 60 min. A venous blood sample was obtained from each participant for genetic analysis. Twenty-eight haplotype-tagging (Tag) SNPs in the GLP-1R locus incorporating 10,000bp upstream and downstream of the major transcription initiation site and the last exon, respectively, were identified from the HapMap database. Twenty-seven SNPs were successfully genotyped using Sequenom MassARRAY iPLEX GOLD analysis. Gastric emptying results were analysed by genotype and phenotype using Kruskal-Wallace and Wilcoxon statistical tests, respectively. Values are median [quartiles].

A significant effect of genotype on time of maximum emptying rate (T_{lag}) was seen for neighbouring SNPs rs742764 and rs2254336. For SNP rs742764, T_{lag} was faster in genotype CC compared to genotype TT and TC (35 [30-36] *vs*. 41 [37-46] and 41 [39-45] min; $P<0.01$). For SNP rs2254336, T_{lag} was slower in genotype AA compared to genotype TT and TA (43 [39-49] *vs.* 36 [34-41] and 39 [35-42] min; $P<0.05$). An effect of phenotype was also seen for SNP rs2254336 where T_{lag} was slower in homozygotes of the major allele A compared to participants with the minor allele T (43 [39-49] *vs*. 39 [34-41] min; $P<0.05$). Further effects of phenotype were seen for SNP rs2268657 where T_{lag} was faster in homozygotes of the major allele A compared to participants with the minor allele G (37 [34-39] *vs*. 41 [37-45] min; $P<0.05$) and for SNP rs9283907 where half emptying time ($T_{½}$) was slower in homozygotes of the major allele G compared to participants with the minor allele A (67 [59-82] *vs.* 55 [53-61] min; $P<0.05$).

The results of this study suggest that gastric emptying rate may be influenced by SNPs within the GLP-1R gene. Replication of this pilot study in larger cohorts is required to confirm the contribution of GLP-1R gene variation to gastric emptying rate.

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