Schizophrenia Research 160 (2014) 73–79

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Glucagon-like peptide 1 receptor (*GLP1R*) haplotypes correlate with altered response to multiple antipsychotics in the CATIE trial

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ARTICLE INFO

Article history:
Received 19 June 2014
Received in revised form 23 September 2014
Accepted 25 September 2014
Available online 18 October 2014

Keywords:
Olanzapine
Perphenazine
Quetiapine
Risperidone
Ziprasidone
Pharmacogenetics
Schizophrenia

ABSTRACT

Glucagon-like peptide 1 receptor (GLP1R) signaling has been shown to have antipsychotic properties in animal models and to impact glucose-dependent insulin release, satiety, memory, and learning in man. Previous work has shown that two coding mutations (rs6923761 and rs1042044) are associated with altered insulin release and cortisol levels. We identified four frequently occurring haplotypes in Caucasians, haplotype 1 through haplotype 4, spanning exons 4–7 and containing the two coding variants. We analyzed response to antipsychotics, defined as predicted change in PANSS-Total (dPANSS) at 18 months, in Caucasian subjects from the Clinical Antipsychotic Trial of Intervention Effectiveness treated with olanzapine (n = 139), perphenazine (n = 78), quetiapine (n = 14), risperidone (n = 143), and ziprasidone (n = 90). Haplotype trend regression analysis revealed significant associations with dPANSS for olanzapine (best p = 0.002), perphenazine (best p = 0.01), quetiapine (best p = 0.008), risperidone (best p = 0.02), and ziprasidone (best p = 0.007). We also evaluated genetic models for the two most common haplotypes. Haplotype 1 (uniquely including the rs1042044 [Leu^{260}] allele) was associated with better response to olanzapine (p = 0.002), and risperidone (p = 0.006), and worse response to perphenazine (p = .03), and ziprasidone (p = 0.003), with a recessive genetic model providing the best fit. Haplotype 2 (uniquely including the rs6923761 [Ser^{168}] allele) was associated with better response to perphenazine (p = 0.001) and worse response to olanzapine (p = .02), with a dominant genetic model providing the best fit. However, *GLP1R* haplotypes were not associated with antipsychotic-induced weight gain. These results link functional genetic variants in *GLP1R* to antipsychotic response.

1. Introduction

While antipsychotics have the potential to greatly reduce psychotic symptoms, no drug is safe and efficacious for all patients. Indeed, the Clinical Antipsychotic Trial of Intervention Effectiveness (CATIE) demonstrated that only about a third of patients achieved a clinically meaningful response when treated with commonly used antipsychotics, and even fewer patients were able to maintain the response for extended periods of time (Das et al., 2012). Despite this lack of universal success for any one drug, some patients did experience significant and sustained symptom relief. The high prevalence of side-effects, particularly weight gain and metabolic syndrome, further complicates treatment. Two of the most efficacious antipsychotics, clozapine and olanzapine, also have the highest incidence and severity of weight gain and associated metabolic side-effects (Das et al., 2012). For both clozapine and olanzapine, symptom improvement correlates with weigh gain, i.e. individuals that gain significant amounts of weight are more likely to respond or have a more robust response than those who do not experience significant gain weight (Ascher-Svanum et al., 2005; Bai et al., 2006). Data from CATIE extend this observation to include other drugs as well (Hermes et al., 2011). Thus, identifying which drug will provide the optimal blend of efficacy and minimal side-effects for a given patient remains challenging.

The glucagon-like peptide 1 (GLP1) and the GLP1 receptor (GLP1R) play multiple roles in modulating weight gain, metabolic status, and stress response. In the intestine and pancreas, activation of GLP1R by GLP1 stimulates insulin release and slows gastric emptying (Shah and Vella, 2014). However, in addition to its prevalence in the gut and pancreas, GLP1R is also expressed in the brain (Brunetti et al., 2008). Animal data suggest that both peripheral administration and central administration of either GLP1 or GLP1R agonists can induce decreased appetite and weight loss (Rupprecht et al., 2013; Hayes, 2012). Hayes provides a thorough review of the potential GLP1R-mediated CNS signaling mechanisms that may impact weight gain through appetite suppression and satiety (Hayes, 2012). Data from human studies supports the use of GLP1R agonists as modifiers of antipsychotic induced weight gain (AIWG). Exenatide and liraglutide, both GLP1R agonists, have been approved for use in the United States. These medications have promise as adjunct therapy for the management of AIWG (Ebdrup et al., 2012; Lykkegaard et al., 2008; Ishoy et al., 2013).

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http://dx.doi.org/10.1016/j.schres.2014.09.038
0920-9964/

In addition to the appetite control mechanisms, GLP1R may play a role in other pathways and mechanisms important for psychosis and antipsychotic response. Specifically, GLP1 signaling impacts hypothalamic–pituitary–adrenal axis (HPA) activation, autonomic stress response and anxiety-related behaviors (Ghosal et al., 2013). For example, GLP1R interacts with several neurotransmitter-related proteins in the brain such as gamma amino butyric acid receptor B2; calcium related proteins neurogranin and calmodulin; and two proteins, synaptogyrin and GPR37 that interact with the dopamine transporter (http://www.ncbi.nlm.nih.gov/gene/2740). Both GLP1 and exenatide stimulate serotonin release from the rat hypothalamus in vitro, which may mediate weight loss through 5HT2C receptor agonism (Brunetti et al., 2008).

Beyond biochemical interactions, in vivo data from animal studies offer intriguing observations regarding the potential utility of GLP1R agonists for treating psychiatric disorders. For example, Graham et al. report that pre-treatment with exenatide can mitigate conditioned place preference (a model for addiction) for cocaine in mice (Graham et al., 2013). Additionally, GLP1R agonists mitigate the effects of both alcohol and amphetamine (Erreger et al., 2012). GLP1R agonists have demonstrated neuroprotective action in model systems for Alzheimer's disease and Parkinson's disease (Holscher, 2014). Moreover, the GLP1R agonist liraglutide shows remarkable antipsychotic-like properties comparable to haloperidol in a mouse model of psychosis (Dixit et al., 2013).

In humans, coding variants in GLP1R have been shown to impact both insulin release and morning cortisol levels. In non-diabetic subjects, genetic variation in GLP1R impacts insulin secretion following exogenous administration of GLP1 (Sathananthan et al., 2010). Subjects homozygous for the major allele of rs6923761 (Gly^{168}) secreted significantly more insulin than subjects containing at least one copy of the minor allele. Another coding variant, rs1042044, has been linked to increased morning cortisol levels in children (Sheikh et al., 2010). Subjects homozygous for the minor allele (Leu^{260}) displayed higher morning cortisol levels, which have been linked to increased risk for major depressive disorder in youths and adults (Bhagwagar et al., 2005; Goodyer et al., 2009; Koole et al., 2011).

Previously, many studies have been published on the efficacy, side-effects, and pharmacogenetics of the CATIE study (Adkins et al., 2011; Hermes et al., 2011; Lieberman et al., 2005; Liu et al., 2012a; Liu et al., 2012b; McClay et al., 2011b; McClay et al., 2011a; Need et al., 2009; Ramsey et al., 2013; Stroup et al., 2007). Given the potential for both metabolic and CNS effects of GLP1R signaling as well as in vitro and in vivo data suggesting that genetic variation in *GLP1R* impacts potentially relevant pharmacogenetic phenotypes, we investigated whether genetic variation in *GLP1R* impacted response to antipsychotics in the CATIE trial. Here we report the findings with a focus on the potential impact of coding variation in the gene.

2. Materials and methods

2.1. Subjects and data

Subjects are those included in the CATIE sample, and the design of the CATIE study has been described in detail elsewhere (Stroup et al., 2003, 2007). Only self described "white" or Caucasian patients were included in the current analysis. Furthermore, only the blinded phases of the study, Phases 1, 1B and 2 were included in the current analysis. In Phase 1, schizophrenia patients were randomly assigned to one of four atypical antipsychotic drugs, olanzapine, quetiapine, risperidone or olanzapine, or to perphenazine, a typical antipsychotic drug. Investigators could elect to switch medication at any time during the 18 month study duration. A drug switch triggered a new randomization to a previously unused study drug. National Institute of Mental Health Center for Collaborative Genetic Studies on Mental Disorders (CGSMD) (https://www.nimhgenetics.org/) provided the genotype and phenotype data used in this study. Table 1 details the distribution of Caucasian subjects by drug across Phases 1, 1B, and 2.

2.2. Haplotype determination

The CATIE data included genotypes from 13 SNPs within the promoter and transcribed region of *GLP1R*: rs10305416, rs910171, rs926674, rs10305439, rs9296283, rs7766275, rs2300615, rs1042044, rs932443, rs2268645, rs10305492, rs1126476, and rs2300612. We determine blocks of linkage disequilibrium (LD) using the default settings of Haploview 4.2 (Broad Institute, Cambridge Ma) for haplotype block determination using the confidence interval method (upper CI: 0.98, lower CI: 0.7, and excluded markers with minor allele frequency < 0.05) (Barrett et al., 2005). To assign haplotypes to individuals, we used the expectation maximization (EM) algorithm function of HelixTree version 6.4.3 (GoldenHelix, Bozeman, MT) on the identified haplotype block (Barrett et al., 2005).

The HapMap CEU data set was used to determine if haplotype blocks identified in the CATIE genotype data (which was genotyped using an older technology) tagged additional coding variant(s) beyond rs1042044. *GLP1R* HapMap data (chromosome 6: 39,048 kb to 39,088 kb GRCh38 primary assembly) was downloaded through Haploview using HapMap version 3 release R2. We determined haplotype blocks using the default settings of Haploview (Broad Institute, Cambridge Ma) for haplotype block definition as described above. As described in the Results, one allele of rs6923761, which was not included in the genotypes provided by CGSMD, is associated exclusively with a particular haplotype in the region ranging from 39,142 kb (rs6923761) to 39,149.5 kb (rs1042044). By comparing the HapMap data to the CATIE data we determined that the coding variant rs6923761 could be uniquely assigned to haplotype 2.

2.3. Definition of response

In order to provide consistent and unbiased definition of response, we used predicted change in Positive and Negative Syndrome Scale Total scores (dPANSS) from using the 30-day lag model developed by van den Oord et al. (2009) (response model). This response model is a mixed model repeated measures (MMRM) model that incorporates baseline, treatment, and response at each time point into the predicted 18 month response. The model provided 18 month predicted dPANSS values for each subject. As baseline response was already included in the response model, it was not used as covariate in the analysis, which predicted dPANSS as the dependent variable.

2.4. Haplotype trend regression

We used the haplotype trend regression (HTR) function in HelixTree to evaluate whether or not haplotypic variation in *GLP1R* was associated with differential responses to the CATIE drugs. HelixTree assigns haplotypes to subjects using the EM algorithm and performs a linear regression with the various haplotypes as independent variables. The dependent variable was dPANSS. To control for multiple testing, we used the Benjamini graphically sharpened false discovery rate method (Benjamini and Hockberg, 2000).

Table 1
Number of subjects in each phase by drug.

	Phase 1/1A	Phase 1B	Phase 2	Total	Mean age, years (SD)	Percent male
Olanzapine	93	10	41	144	40.3 (11.5)	74
Perphenazine	78			78	41.2 (11.1)	81
Quetiapine	95	16	30	141	41 (10.3)	80
Risperidone	97	12	34	143	41.5 (11)	76
Ziprasidone	49		42	91	39.2 (11.5)	74
Total	412	38	147	597	40.7 (11)	77