

Exploring genetic variations that may be associated with the direct effects of some antipsychotics on lipid levels

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Abstract

The goal of this study was to select some genes that may serve as good candidates for future studies of the direct effects (not explained by obesity) of some antipsychotics on hyperlipidemia. A search for single-nucleotide polymorphisms (SNPs) that may be associated with these direct effects was conducted. From a published cross-sectional sample, 357 patients on antipsychotics were genotyped using a DNA microarray with 384 SNPs. A total of 165 patients were taking olanzapine, quetiapine or chlorpromazine which may directly cause hypertriglyceridemia or hypercholesterolemia. Another 192 patients taking other antipsychotics were controls. A two-stage statistical analysis that included loglinear and logistic models was developed to select SNPs blindly. In a third stage, physiological knowledge was used to select promising SNPs. Known physiological mechanisms were supported for 3 associations found in patients taking olanzapine, quetiapine or chlorpromazine [acetyl-coenzyme A carboxylase α SNP (rs4072032) in the hypertriglyceridemia model, and for the neuropeptide Y (rs1468271) and ACC β , (rs2241220) in the hypercholesterolemia model]. These genes may be promising candidates for studies of the direct effects of some antipsychotics on hyperlipidemia.

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1. Introduction

The variability of individual responses and the high prevalence of metabolic syndrome observed in the Clinical

Antipsychotic Trials of Intervention Effectiveness (CATIE) study (Lieberman et al., 2005) indicate the need to consider personalized prescriptions for antipsychotics (de Leon and Diaz, 2007), which may become cost-effective due to decreasing genotyping costs and marketing of generic forms of some atypical antipsychotics (Ruaño et al., 2007).

Clinical experience (Markham-Abedi and de Leon, 2006) and a literature review (de Leon and Diaz, 2007) led us to hypothesize that antipsychotics may cause

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hyperlipidemia (hypertriglyceridemia or hypercholesterolemia) through two possible mechanisms: (1) an indirect mechanism, associated with weight gain, that leads to obesity and in the long term causes hyperlipidemia; and (2) a direct mechanism by which some antipsychotics (particularly clozapine and olanzapine, and possibly quetiapine and low-potency typical antipsychotics; Meyer and Koro, 2004) can directly cause hyperlipidemia. A shared antipsychotic chemical structure may explain these direct effects (de Leon and Diaz, 2007), which occur quickly (a few weeks after antipsychotic initiation) and disappear quickly after discontinuation (Markham-Abedi and de Leon, 2006). Cross-sectional lipid studies can detect these rapid direct effects (de Leon and Diaz, 2007).

In the current study, 357 severely mentally ill patients on antipsychotics from a published hyperlipidemia study (de Leon et al., 2007) were genotyped using a DNA microarray. The goal was to select some genes that may serve as good candidates for future studies of the direct effects (not explained by obesity) of some antipsychotics on hyperlipidemia (hypertriglyceridemia or hypercholesterolemia). To achieve this goal, a search for single-nucleotide polymorphisms (SNPs) that may be associated with these direct effects was conducted. It was hypothesized that olanzapine, quetiapine and chlorpromazine may increase lipids directly. Other antipsychotics served as controls.

2. Methods

2.1. Sample

The genotyped patients included 165 on olanzapine, quetiapine or chlorpromazine, and 192 on other antipsychotics (risperidone, ziprasidone, aripiprazole, or typicals other than chlorpromazine). As previously described (de Leon et al., 2007), the patients were taking only one antipsychotic, with the exception of some of the patients on olanzapine and some patients who were taking more than one typical antipsychotic. The mean age was 37.6 years (standard deviation, SD 10.6); 64% (229/357) of the patients were male and 88% (315/357) were US Caucasian. Written informed consent was obtained after completely describing the study to the subjects.

2.2. Assessments

All patients were assessed for serum glucose, total cholesterol, HDL cholesterol and triglyceride levels in a cross-sectional design. The mean \pm SD cholesterol levels

were 192 ± 52 mg/dl in 56 patients taking olanzapine, 194 ± 46 mg/dl in 104 patients taking only quetiapine, and 183 ± 33 mg/dl in 5 patients taking only chlorpromazine. The mean \pm SD triglyceride levels were 202 ± 124 mg/dl in patients taking olanzapine, 224 ± 134 mg/dl in patients taking only quetiapine, and 231 ± 144 mg/dl in patients taking chlorpromazine. Thus, these results support the inclusion of chlorpromazine as a hyperlipidemic antipsychotic. This inclusion is also supported by the literature (Sasaki et al., 1985; Meyer and Koro, 2004). Obesity was measured in three ways: by the body mass index, by the Tanita scale which uses foot-to-foot bioelectrical impedance to estimate body fat percentage, and by the waist circumference (de Leon et al., 2007). From these three obesity measures, linear regression analyses suggested that body fat percentage and waist circumference were the best predictors for cholesterol and triglyceride levels, respectively (de Leon et al., 2007).

Hypertriglyceridemia was defined as having a triglyceride level ≥ 150 mg/dl (Ford et al., 2002) or undergoing current treatment for hyperlipidemia, and hypercholesterolemia as having a total cholesterol level ≥ 240 mg/dl (Pearson, 2004) or undergoing current treatment for hyperlipidemia.

Genotyping was performed using the Illumina BeadArray™ platform and the GoldenGate™ assay. The Genomas gene array (Patent Application Publication US 2006/0234262A1) includes 384 single-nucleotide polymorphisms (SNPs) from 215 genes representing cardiovascular physiology, inflammation, neurobiology, metabolism, cholesterol biochemistry, and cell proliferation) (see Table 1, Footnote a).

2.3. Statistics

A two-stage statistical approach including a loglinear analysis (Agresti, 1990; R Development Core Team, 2005) stage and a logistic regression analysis (Woodward, 1999; SPSS, Inc., 1997) stage was developed to explore the 384 SNPs. For each SNP, the minor-frequency allele was determined and the total number of minor-frequency alleles in each patient was computed. Thus, the computed number for each patient was 0, 1 or 2. For each SNP, a reference number was selected. The logistic analyses compared the odds of hypertriglyceridemia (or severe hypercholesterolemia) having a particular number versus the odds of having the SNP's reference number. Table 1 describes in detail how the reference number was selected for each SNP according to number frequencies. The goal was to identify SNPs statistically associated with hypertriglyceridemia or

severe hypercholesterolemia in the patients taking the antipsychotics of interest (olanzapine, quetiapine or chlorpromazine), after controlling for the confounding effects of obesity (de Leon et al., 2007). In a third stage, the biological plausibility of the identified SNPs was considered by reviewing known physiological mechanisms.

To identify SNPs possibly associated with hypertriglyceridemia in patients on the antipsychotics of interest, in the first stage loglinear models were fit in males and females separately and for each SNP. Since loglinear models only use categorical variables, the waist circumference variable was dichotomized in males (>102 vs. ≤102 cm) and females (>88 vs. ≤88 cm) (Ford et al., 2002). The age variable was dichotomized as ≥35 vs. <35 years. Each loglinear model included the following variables: the SNP as a categorical variable (0, 1 or 2 minor-frequency alleles), hypertriglyceridemia, and the dichotomized waist circumference and age. Each model represented conditional independence of the SNP and hypertriglyceridemia

after adjusting for waist circumference and age. The null hypothesis of conditional independence was tested in each of the 2 models by using a goodness-of-fit G^2 test. If at least one of the 2 p -values was <0.1, then the SNP entered the logistic regression stage; if the 2 p -values were ≥0.1, no further explorations were performed with the SNP. An advantage of using these models is that they do not assume lack of interaction, which allows dealing with unknown relationships between the variables included in the model.

In the second stage, a backward selection procedure was used to obtain the best logistic regression model, using hypertriglyceridemia as the dependent variable. The independent variables tested were waist circumference and age as continuous measures, gender, and the SNPs that produced at least one p -value <0.1 in the first stage. A similar two-stage approach was used to find the SNPs possibly associated with severe hypercholesterolemia in patients on antipsychotics of interest, although percentage of body fat was used in place of waist circumference to control for obesity (de Leon et al., 2007). To perform

Table 1

Comparison of effect sizes of SNPs^a potentially associated with hypertriglyceridemia or hypercholesterolemia in patients taking olanzapine, quetiapine or chlorpromazine ($N=165$) versus others (risperidone, ziprasidone, aripiprazole, or typicals other than chlorpromazine; $N=192$)

	Olanzapine, quetiapine or chlorpromazine			Other antipsychotics		
	OR	95% CI	p	OR	95% CI	p
HYPERTRIGLYCERIDEMIA^{b,c}						
Transforming growth factor β 1 (Exon 1, aa substitution: R25P)						
rs1800471 (1) ^{d,e}	0.23^f	0.074–0.70	0.009	0.78 ^g	0.30–2.1	0.6
Acetyl-coenzyme A carboxylase α , ACC α (Exon 13, synonymous substitution: Q604Q) ^h						
rs2229416 (2) ⁱ	2.5^f	1.03–6.2	0.04	1.3 ^g	0.62–2.8	0.5
Platelet/endothelial cell adhesion molecule 1, PECAM-1 (Intron 1) ^h						
rs4072032			0.03			0.3
rs4072032 (0) ^d	0.63^f	0.25–1.6		0.58 ^g	0.23–1.5	
rs4072032 (1) ^d	2.5^f	0.96–6.3		0.58 ^g	0.28–1.2	
Amiloride binding protein 1 (Exon 3, aa substitution: D645H)						
rs1049793			0.04			0.007
rs1049793 (0) ^d	0.21^f	0.06–0.72		1.5^j	0.57–4.1	
rs1049793 (1) ^d	0.88^f	0.39–1.99		3.1^j	1.5–6.3	
Angiotensin I converting enzyme (4kbp upstream) ^k						
rs1800764			0.14			0.009
rs1800764 (0) ^d	2.8 ^l	0.85–9.1		2.5^j	1.1–5.8	
rs1800764 (1) ^d	2.4 ^l	0.92–6.2		3.7^j	1.6–8.5	
Waist circumference	1.04^f	1.01–1.06	0.007	1.04^j	1.02–1.06	0.001
HYPERCHOLESTEROLEMIA^{m,n}						
Neuropeptide Y, NPY (Intron 1) ^h						
rs1468271 (0) ^o	0.22^p	0.06–0.81	0.02	1.02 ^q	0.19–5.6	0.98
Acetyl-coenzyme A carboxylase β , ACC β (Exon 32, aa substitution: L1582L)						
rs2241220 (2) ^r	0.40^p	0.17–0.92	0.03	0.74 ^q	0.31–1.8	0.5
Angiotensinogen proteinase inhibitor (Exon 1, aa substitution: M207T)						
rs4762 (1) ^{d,s}	3.1^p	1.2–8.0	0.02	0.67 ^q	0.30–1.5	0.3
% of body fat	1.05^p	1.02–1.09	0.005	1.02 ^q	0.99–1.06	0.3
Age	1.05^p	1.009–1.1	0.02	1.09^t	1.04–1.14	<0.001

loglinear analyses, body fat percentage was dichotomized in males (≥ 26 vs. $<26\%$) and females (≥ 39 vs. $<39\%$) according to Receiver Operating Characteristic (ROC; Woodward, 1999) analyses using the clinical definition of obesity. Analogous analyses were performed in patients on other antipsychotics.

The first two stages of the analyses were developed blindly in reference to the genes behind the SNP identification code. Table 1 describes all significant SNPs after the second stage. As with any complex statistical approach exploring genetic associations, it was expected that the two-stage approach would provide false positive associations. Thus, known physiological mechanisms were used as an index of biological plausibility in a third-stage

selection process that was intended to select promising SNPs for future studies.

3. Results

3.1. SNPs associated with hypertriglyceridemia

Three SNPs in 3 different genes (transforming growth factor $\beta 1$; acetyl-coenzyme A carboxylase α , ACC α ; and platelet/endothelial cell adhesion molecule 1, PECAM-1) were significant in the logistic regression model obtained for patients on antipsychotics of interest, but not in that for patients on other antipsychotics (Table 1). The odds ratios (ORs) for these

Notes to Table 1:

OR: Odds ratio; CI: Confidence interval. Significant results are in **bold**. aa substitution: aminoacid substitution.

^a SNP genotypes were coded according to the number of minor-frequency alleles: 0 for major homozygotes, 1 for heterozygotes, and 2 for minor homozygotes. A number in brackets is the number of minor-frequency alleles that is compared with the reference number or numbers. The following pathways are represented in the SNP array: insulin resistance, glucose metabolism, energy homeostasis, adiposity, apolipoproteins and receptors, fatty acids and cholesterol metabolism, lipases and receptors, cell signaling and transcriptional regulation, growth factors, drug metabolism, blood pressure, vascular signaling, endothelial dysfunction, coagulation and fibrinolysis, vascular inflammation, cytokines, neurotransmitter systems (serotonin, dopamine, cholinergic, histamine, glutamate) and behavior (satiety).

^b A backward selection procedure that used patients on olanzapine, quetiapine or chlorpromazine, and hypertriglyceridemia as the dependent variable, selected rs1800471, rs2229416, rs4072032, rs1049793 and waist circumference. Thus, at a 0.05 level of significance, these variables have a significant effect on hypertriglyceridemia after adjusting for each other. Gender and age were not selected by the procedure.

^c A backward selection procedure that used patients on other antipsychotics, and hypertriglyceridemia as the dependent variable, selected rs1049793, rs1800764 and waist circumference. Thus, at a 0.05 level of significance, these variables have a significant effect on hypertriglyceridemia after adjusting for each other. Gender and age were not selected by the procedure.

^d The reference number of minor-frequency alleles is 2.

^e All patients had at least one minor-frequency allele on the SNP, rs1800471.

^f The OR and its corresponding CI is adjusted for the other variables selected by the backward selection procedure that used patients on olanzapine, quetiapine or chlorpromazine, and hypertriglyceridemia as the dependent variable.

^g The OR and its corresponding CI is adjusted for only the variables selected by the backward selection procedure that used patients on other antipsychotics, and hypertriglyceridemia as the dependent variable.

^h There is a possibility that this SNP is involved in promoter or RNA processing.

ⁱ The reference number of minor-frequency alleles is 0 or 1. (Only 2 patients had a null number of minor-frequency alleles; thus, patients with 0 or 1 allele were combined together.)

^j The OR and its corresponding CI is adjusted for the other variables selected by the backward selection procedure that used patients on other antipsychotics, and hypertriglyceridemia as the dependent variable.

^k There is a possibility that the SNP is located at the promoter site.

^l The OR and its CI is adjusted for the variables selected by the backward selection procedure that used patients on olanzapine, quetiapine or chlorpromazine, and hypertriglyceridemia as the dependent variable.

^m A backward selection procedure that used patients on olanzapine, quetiapine or chlorpromazine, and hypercholesterolemia as the dependent variable, selected rs1468271, rs2241220, rs4762, percentage of body fat and age. Thus, at a 0.05 level of significance, these variables have a significant effect on hypercholesterolemia after adjusting for each other. Gender was not selected by the procedure.

ⁿ A backward selection procedure that used patients on other antipsychotics, and hypercholesterolemia as the dependent variable, selected only age. Thus, at a 0.05 level of significance, age has a significant effect on hypercholesterolemia. No SNP was selected, nor gender or percentage of body fat.

^o None of the patients had 2 minor-frequency alleles on the SNP, rs1468271. The reference number of alleles was set to 1.

^p The OR and its corresponding CI is adjusted for the other variables selected by the backward selection procedure that used patients on olanzapine, quetiapine or chlorpromazine, and hypercholesterolemia as the dependent variable.

^q The OR and its corresponding CI is adjusted for age.

^r The reference number of minor-frequency alleles is 0 or 1. (Only 6 patients had a null number of minor-frequency alleles; thus, patients with 0 or 1 allele were combined together.)

^s All patients had at least one minor-frequency allele on the SNP, rs4762.

^t Since the backward selection procedure that used patients on other antipsychotics, and hypercholesterolemia as the dependent variable, selected only age, this OR was not adjusted for any other variable.

SNPs remained essentially the same after excluding non-Caucasian patients and patients on hyperlipidemia treatment from the former model, ruling out race and hyperlipidemia treatment as possible confounders. The obtained model was fitted using patients on olanzapine and patients on quetiapine separately. The ORs yielded by the 2 models were not significantly different, which is consistent with the hypothesis that these two antipsychotics increase triglycerides similarly.

A SNP in the amiloride binding protein 1 gene was significant in both patient groups, but the 2 groups exhibited opposite ORs (Table 1). A SNP in the angiotensin I converting enzyme gene was significant in the control antipsychotics but not in the antipsychotics of interest, suggesting that this SNP may not be involved in the direct effects of the antipsychotics of interest.

3.2. SNPs associated with hypercholesterolemia

The obtained logistic model for patients on the antipsychotics of interest included 3 SNPs in 3 different genes (neuropeptide Y, NPY; ACC β ; and angiotensinogen proteinase inhibitor), which were not included in the model for patients on other antipsychotics. The corresponding ORs for patients on olanzapine and on quetiapine were not significantly different from each other, and further analyses ruled out race and hyperlipidemia treatment as confounders.

4. Discussion

4.1. SNPs associated with hypertriglyceridemia

In patients on olanzapine, quetiapine or chlorpromazine, the SNPs in the transforming growth factor β 1, ACC α , and PECAM-1 genes had significant associations with hypertriglyceridemia after controlling for obesity. These SNPs were not significantly associated with hypertriglyceridemia in patients on other antipsychotics. This is consistent with the idea that these SNPs may be involved in the direct effects of olanzapine, quetiapine or chlorpromazine on triglyceride levels. However, the biological plausibility of these significant associations must be examined.

The association of an ACC α gene variation with hypertriglyceridemia fits with known physiological mechanisms since ACC α is the rate-limiting enzyme in the synthesis of long-chain fatty acids, and its inhibitors may be potential metabolic syndrome treatments (Harwood, 2005). The biological mechanisms of this association may be studied by testing whether

olanzapine, quetiapine, chlorpromazine, and possibly clozapine modify the action of this enzyme. Genetic variations may confer different sensitivity to these antipsychotics.

The transforming growth factor β 1 is a multifunctional cytokine that exhibits vasculoprotective properties and has no obvious involvement in lipid metabolism, suggesting that an association between this gene and hypertriglyceridemia may be biologically implausible. However, some of its gene variations were associated with myocardial infarction (Koch et al., 2006). Similarly, an association of PECAM-1 with hypertriglyceridemia is hardly plausible, since PECAM-1 is a member of the immunoglobulin superfamily expressed in blood cells.

4.2. SNPs associated with hypercholesterolemia

The SNPs on the NPY and ACC β genes may be associated with known physiological mechanisms affecting cholesterol levels. NPY polymorphisms were associated with serum cholesterol levels in several studies and with cerebrospinal-fluid cholesterol levels in an Alzheimer study (Kolsch et al., 2006). NPY is a potent stimulator of food intake and influences lipid metabolism. The injection of NPY in the hypothalamus results in pronounced hyperphagia. In starvation states, NPY expression and release is elevated while circulating levels of leptin and insulin are low. NPY expression is inhibited by both leptin and insulin. Obese mice lacking leptin display high NPY activity in the hypothalamus, which is corrected by leptin administration (Turtzo and Lane, 2006). A recent study has explored the association of leptin and leptin receptor genes with olanzapine-induced weight gain (Ellingrod et al., 2007).

ACC β appears to be involved in mitochondrial fatty oxidation and produces malonyl-CoA, which may act centrally to control food intake through production of hypothalamic NPY (Harwood, 2005). It is very interesting that in our results, an ACC α gene variation predicted hypertriglyceridemia while an ACC β gene variation predicted hypercholesterolemia. Knockout mouse models suggest that ACC α has a fundamental role in fatty acid synthesis while ACC β has a less basic role but influences appetite and lipid metabolism in complex ways. A homozygous deficiency of ACC α causes fetal lethality in mice, which indicates that ACC α has a basic role in fatty acid synthesis. The ACC β null mouse is hyperphagic and has reduced body fat indicating a complex ACC β role associated with behavioral effects (Kusunoki et al., 2006).

Angiotensinogen proteinase inhibitor is a protease inhibitor with largely unknown functions and low

biological plausibility of being associated with cholesterol levels.

4.3. Limitations

This study has all the limitations of exploratory genetic studies using naturalistic samples, although potential confounders (gender, age, race, and, more importantly, obesity) were carefully controlled. It was not possible to control for antipsychotic treatment duration but in this cross-sectional study we were confident that we could detect the rapid direct effects of antipsychotics on lipid levels (de Leon et al., 2007), which appear to develop in a few weeks (de Leon and Diaz, 2007). Other co-medications probably have no important effects on hyperlipidemia not explained by obesity. Mood stabilizers do not directly increase lipid levels. In fact, they may decrease lipid levels (de Leon and Diaz, 2007). The only other psychiatric drug that may have direct effects on lipids (de Leon and Diaz, 2007) and may have contaminated this study was mirtazapine, which was currently taken by 5% of the patients on olanzapine, quetiapine or chlorpromazine, versus 7% of the others.

This study did not make corrections for the multiple comparisons performed. However, the literature does not provide definitive and widely accepted guidelines on how to deal with significant results from multiple comparisons in exploratory genetic studies. The position adopted in this study is that statistical methods are just exploratory tools whose results must be carefully examined for biological and clinical plausibility. Also, even if a study finds a very small *p*-value for the association between a gene variant and a disease, the clinical importance of the association should be assessed, and additional studies should be designed with the purpose of replicating the association. The authors have argued that a pharmacogenetic test may be more useful in the clinical environment if it is based on gene variants with large effect sizes and if the gene effects have been replicated in a variety of clinical settings (de Leon and Diaz, 2007).

5. Conclusions

If some antipsychotics have direct effects on hyperlipidemia, then these effects may be influenced by some genetic variations. Our three-stage approach suggested that ACC α , ACC β , and NPY genes may be good candidates for studies of the direct effects of some antipsychotics on hyperlipidemia. Future studies of these genes should include more systematic SNP

assessments and haplotypes, to better reflect gene function.

Role of the funding source

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Contributors

Jose de Leon, M.D., designed the study. Juan Carlos Correa, Ph.D., and Francisco J. Diaz, Ph.D., undertook the statistical analyses helped by Jose de Leon, M.D. Jose de Leon, M.D., wrote the first draft of the manuscript. All authors have contributed to and have approved the final manuscript.

Conflict of interest

In the past three years, Jose de Leon, M.D., has been on the advisory board of Roche Molecular Systems, Inc., and Bristol Myers and Squibb; he received investigator-initiated grants from Roche Molecular Systems, Inc., and Eli Lilly Research Foundation; he has lectured twice supported by Eli Lilly, twice by Janssen, and six times by Roche Molecular Systems, Inc. Juan Carlos Correa, Ph.D., has no conflict of interest. Gualberto Ruaño, M.D., Ph.D., and Andreas Windemuth, Ph.D., work at Genomas, Inc, a pharmacogenetic company interested in the metabolic syndrome and supported by a NIH Small Business Innovation Research Grant 1 R43 MH073291-01 "Gene Markers: Antipsychotic-Induced Metabolic Syndrome." Maria J. Arranz, Ph.D., is a consultant for the company TheraGenetics (UK), and actively collaborates with the company LGC (UK) in the development of genetic tests. Dr. Arranz has received consultancy money from LGC. In the past three years, Francisco J. Diaz, Ph.D., has been a statistical consultant for an investigator-initiated Eli Lilly Research Foundation grant in which Dr. de Leon was a co-investigator.

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