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Acetyl-coenzyme A carboxylase α gene variations may be associated with the direct effects of some antipsychotics on triglyceride levels

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ABSTRACT

Acetyl-coenzyme A carboxylase α (ACACA) single-nucleotide polymorphism (SNP) (rs2229416) was significantly associated with hypertriglyceridemia, during exploration of antipsychotic direct effects on lipids. Neuropeptide Y (*NPY*) gene (rs1468271) and *ACACB* gene (rs2241220) SNPs were significantly associated with severe hypercholesterolemia. In the same sample (173 patients on olanzapine, quetiapine, chlorpromazine or mirtazapine [increasing the risk of hyperlipidemia] and 184 controls taking other antipsychotics), three (rs1266175, rs12453407 and rs9906543) of eight additional ACACA SNPs were significantly associated with hypertriglyceridemia in those taking drugs of interest, but not in controls. Five other ACACA SNPs, three additional NPY SNPs, and seven additional ACACB SNPs were not significant.

1. Introduction

Based on clinical experience (Markham-Abedi and de Leon, 2006) and study reports (Meyer and Koro, 2004), we hypothesized that antipsychotics may cause hyperlipidemia (hypertriglyceridemia or hypercholesterolemia) through two possible mechanisms: (1) an indirect mechanism, mediated by a substantial weight gain, which causes hyperlipidemia in the long term, and (2) a direct mechanism by which some antipsychotics (particularly clozapine, olanzapine, quetiapine and phenothiazines) can directly cause hyperlipidemia (de Leon and Diaz, 2007). A shared chemical structure may explain these particular antipsychotics' direct effects (de Leon and Diaz, 2007) and why mirtazapine may have similar effects (Chen et al., 2003; de Leon, 2008). These direct effects on lipids are not explained by obesity, occur quickly (a few weeks after antipsychotic initiation), and disappear quickly

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after discontinuation (Markham-Abedi and de Leon, 2006). Cross-sectional lipid studies can detect these rapid effects (de Leon and Diaz, 2007).

By using a DNA microarray that incorporated 384 single-nucleotide polymorphisms (SNPs) (Ruaño et al., 2007), we searched for candidate genes that may explain the direct effects of some antipsychotics (olanzapine, quetiapine and chlorpromazine) on lipids (de Leon et al., 2008). We found that an acetyl-coenzyme A carboxylase α (ACACA) SNP (rs2229416) was significantly associated with hypertriglyceridemia in 165 patients who were taking the above antipsychotics. Two other SNPs, one in the neuropeptide Y (*NPY*) gene (rs1468271) and the other in the acetyl-coenzyme A carboxylase β (*ACACB*) gene (rs2241220), were significantly associated with severe hypercholesterolemia in the same patients. Since these associations were not significant in 192 patients on other antipsychotics that do not tend to affect lipids and the confounding effect of obesity was controlled, we concluded that the *ACACA*, *NPY* and *ACACB* genes may be good candidates for further studies, given that these exploratory analyses used only one SNP per gene. Other genes emerged from the statistical analyses, but only these three seemed biologically plausible mediators in antipsychotic-induced hyperlipidemia.

The goal of this study was to explore additional SNPs in the *ACACA*, *NPY* and *ACACB* genes, in an attempt to further substantiate the claim that some of these genes may be involved in the direct effects of some antipsychotics on hyperlipidemia.

2. Methods

2.1. Sample

The cross-sectional sample has been described previously (de Leon et al., 2007, 2008); it included 357 patients taking antipsychotics. The mean ± SD age was 37.6 ± 10.6 years; 64% were male; and 88% were US Caucasian. Written informed consents were obtained.

In these new analyses the sample was divided into 173 patients taking drugs that increase the risk of hyperlipidemia (olanzapine, quetiapine, chlorpromazine or mirtazapine) and 184 controls taking other antipsychotics (risperidone, aripiprazole, ziprasidone and typicals other than phenothiazines). Olanzapine, quetiapine and chlorpromazine are potent H1 blockers. H1 blocking properties are probably the main reason why these antipsychotics are associated with weight gain (Matsui-Sakata et al., 2005). Antipsychotics with high affinity for H1 receptors may have something in their chemical structure that makes them particularly prone to interfere directly with lipid metabolism. Mirtazapine is an antidepressant that has high affinity for H1 receptors, thereby causing weight gain (Himmerich et al., 2006). We have proposed that mirtazapine is likely to have direct effects on lipid metabolism similar to those of antipsychotics with high H1 affinity (de Leon, 2008). The mean ± SD triglyceride levels were 202 ± 122 mg/dl in 57 patients on olanzapine, 225 ± 134 in 105 on only quetiapine, 231 ± 144 in 5 on chlorpromazine, 262 ± 198 in 8 on both mirtazapine and non-H1 blocking antipsychotics, and 167 ± 95 in 185 on non-H1 blocking antipsychotics but not taking mirtazapine. The mean ± SD cholesterol levels were 192 ± 52 mg/dl in 57 patients on olanzapine, 194 ± 46 in 105 patients on quetiapine, 183 ± 33 in 5 on chlorpromazine, 205 ± 16 in 8 on both mirtazapine and non-H1 blocking antipsychotics, and 177 ± 38 in 185 on non-H1 blocking antipsychotics but not taking mirtazapine.

2.2. Assessments

All patients were assessed for total cholesterol, HDL cholesterol and triglyceride levels. As measures of obesity we used body fat percentage (measured by the Tanita scale) or waist circumference (de Leon et al., 2007). Following de Leon et al. (2008), these measures were used to control for obesity in hypercholesterolemia and hypertriglyceridemia analyses, respectively. Severe hypercholesterolemia was defined as having a total cholesterol level ≥ 240 mg/dl or undergoing current treatment for hyperlipidemia; hypertriglyceridemia was defined as having a triglyceride level ≥ 150 mg/dl or undergoing current treatment for hyperlipidemia.

The additional SNPs in the *ACACA*, *NPY* and *ACACB* genes were selected from the HapMap. It provided the best map of those genes meeting the criteria of $R^2 = 0.8$ and a minimum allelic frequency of 20%. Eight SNPs were selected in the *ACACA* gene (rs1266175, rs7208415, rs725038, rs9906543, rs4794750, rs12453407, rs4795194 and rs11650168), 3 in the *NPY* gene (rs16145, rs16478 and rs16141), and 7 in the *ACACB* gene (rs741402, rs2268391, rs2268387, rs2239608, rs3742026, rs7974040 and rs2268384). Genotyping was carried out using the Amplifluor® FAM-JOE Genotyping System.

2.3. Statistics

For each additional ACACA SNP, a logistic regression model of hypertriglyceridemia was fit using the patients taking the drugs of interest (olanzapine, quetiapine, chlorpromazine or mirtazapine). The dependent variable of the model was hypertriglyceridemia. As independent variables, the model included the ACACA SNP, waist circumference [dichotomized in males: >102 (long) vs. ≤102 cm; and females: >88 (long) vs. ≤88 cm], gender, age and Caucasian race. Once the model was fit, the non-significant independent variables were eliminated backwardly (Woodward, 2005). Analogous models were fit using the control sample of patients taking other antipsychotics. Table 1 shows the final models for the 3 ACACA SNPs that reached significance in the patients taking the antipsychotics of interest but did not reach significance in the control sample.

For the additional NPY and ACACB SNPs, logistic regression models of hypercholesterolemia were fit following a procedure analogous to that described above for the ACACA SNPs. Following prior statistical analyses (de Leon et al., 2008), severe hypercholesterolemia and body fat percentage (dichotomized in males: ≥26 vs. <26%; and females: ≥39 vs. <39%) were used in place of hypertriglyceridemia and waist circumference, respectively. The goal was to find the SNPs that were significantly associated with hypercholesterolemia in the patients taking the antipsychotics of interest but not significantly associated with hypercholesterolemia in the control sample.

Table 1
ACACA SNPs significantly associated with hypertriglyceridemia in patients taking olanzapine, quetiapine, chlorpromazine or mirtazapine, according to multivariate logistic regressions. [a]

SNP	All patients ($N=173$)			Excluding patients on mirtazapine ($N=152$)		
	p	OR	95% CI	p	OR	95% CI
rs12453407 [b, c, j]	0.003			0.02 [d, e]		
rs12453407 (0)	NS			NS		
rs12453407 (1)	0.04	2.6	1.1–6.2	NS		
rs1266175 [b, f, j]	0.02			0.02 [g]		
rs1266175 (0)	NS			NS		
rs1266175 (1)	0.006	3.6	1.4–8.8	0.005	3.9	1.5–10.3
rs9906543 [b, h, j]	0.045			0.07 [i]		
rs9906543 (0)	0.04	2.5	1.03–6.3	0.04	2.9	1.1–7.6
rs9906543 (1)	0.02	3.1	1.2–7.8	0.04	2.8	1.1–7.4

OR: Odds ratio; CI: Confidence interval; NS: Not significant. The reference level in all SNPs was having two minor-frequency alleles.

[a] None of the SNPs described in the table was significantly associated with hypertriglyceridemia in a control sample of patients taking other antipsychotics ($N=184$), after adjusting for potential confounders.

[b] SNP genotypes were coded according to the number of minor-frequency alleles: 0 for major homozygotes, 1 for heterozygotes, and 2 for minor homozygotes. For OR computations, the reference number of minor-frequency alleles was 2. Numbers in brackets represent the number of minor-frequency alleles being compared with this reference number.

[c] Other significant independent variables in the logistic model were: large waist circumference (OR = 2.8, 1.3–6.1; $p=0.008$) and male gender (OR = 3.4, 1.5–7.7; $p=0.004$). This SNP (rs12453407) is an intronic SNP. According to the HapMap project, the minor allele frequency in the Caucasian population is 47%.

[d] When the reference number of minor-frequency alleles was set to 0, heterozygous subjects were significantly different from major homozygotes after adjusting for large waist circumference and gender (OR = 3.5, 1.4–8.5; $p=0.006$).

[e] Other significant independent variables in the logistic model were: large waist circumference (OR = 2.8, 1.2–6.5; $p=0.01$) and male gender (OR = 3.4, 1.4–7.9; $p=0.005$).

[f] Other significant independent variables in the logistic model were: large waist circumference (OR = 3.0, 1.4–6.4; $p=0.005$) and male gender (OR = 2.7, 1.2–6.1; $p=0.01$). According to the HapMap project, the minor allele frequency in the Caucasian population is 40%.

[g] Other significant independent variables in the logistic model were: large waist circumference (OR = 2.9, 1.3–6.6; $p=0.01$) and male gender (OR = 3.1, 1.3–7.3; $p=0.01$).

[h] Other significant independent variables in the logistic model were: large waist circumference (OR = 2.9, 1.4–6.2; $p=0.005$) and male gender (OR = 2.4, 1.1–5.3; $p=0.03$). According to the HapMap project, the minor allele frequency in the Caucasian population is 36%.

[i] Other significant independent variables in the logistic model were: large waist circumference (OR = 2.9, 1.3–6.4; $p=0.01$) and male gender (OR = 2.5, 1.1–5.8; $p=0.03$).

[j] The originally assessed SNP (rs2229416) is located in the coding region of the gene. There are a large number of alternative transcripts for ACACA in the GenBank database, with respect to most of which rs2229416 is a synonymous substitution. However, there is one reported transcript (NP_942133) within which rs2229416 constitutes an Asp ->Asn amino acid substitution at position 529 in the protein product. The three SNPs found in the current analysis (rs12453407, rs1266175 and rs9906543) are all intronic. According to HapMap linkage data, the entire gene region of ACACA is under strong linkage disequilibrium in the Caucasian population. The strongest predictor in Table 1 (rs12453407) is also the one closest to rs2229416, approximately 20kb downstream. In between these two loci, approximately 10 kb downstream of rs2229416, there are 3 coding SNPs listed in dbSNP: rs17848759, rs2287351, and rs17848757, neither of which has heterozygosities listed in the database. With respect to protein translation NP_942131.1, these SNPs code for substitutions Asp917His, Arg875Trp, and Pro874Ser. These have to be considered prime candidates for the actual causative variation that led, via linkage disequilibrium, to the variations we observed in the present studies.

3. Results

3.1. ACACA gene and hypertriglyceridemia

After adjusting for gender and long waist circumference, three of the 8 additional ACACA SNPs were significantly associated with hypertriglyceridemia in the patients taking olanzapine, quetiapine, chlorpromazine or mirtazapine (rs1266175, rs12453407 and rs9906543; Table 1). These associations were not significant in the control patients taking other antipsychotics. The other 5 ACACA SNPs (rs7208415, rs725038, rs4794750, rs4795194 and rs11650168) were not significantly associated with hypertriglyceridemia in either sample. Following one reviewer's recommendation the analyses were repeated after excluding mirtazapine patients, obtaining essentially the same results as above (Table 1).

3.2. NPY and ACACB genes and hypercholesterolemia

After adjusting for age and high body fat percentage, none of the 3 additional NPY SNPs and none of the 7 additional ACACB SNPs were significantly associated with severe hypercholesterolemia in the patients taking olanzapine, quetiapine, chlorpromazine or mirtazapine. Likewise, no association was observed in the control sample.

4. Discussion

4.1. Verification of significant associations of additional ACACA SNPs with hypertriglyceridemia

We found a SNP in the *ACACA* gene (rs2229416) that was significantly associated with hypertriglyceridemia in patients taking H1 antagonists which may have direct effects on hyperlipidemia (de Leon et al., 2008). Since this association was not explained by obesity or other confounding variables and was not observed in patients taking other antipsychotics, and given that ACACA is the rate-limiting enzyme in the synthesis of long-chain fatty acids and that its inhibitors may be potential metabolic syndrome treatments (Harwood, 2005), it was hypothesized that the *ACACA* gene may be involved in these direct effects. Interestingly, this hypothesis was supported by 3 other ACACA SNPs that were tested in the lab after formulating the hypothesis (rs12453407, rs1266175 and rs9906543; Table 1).

Additionally, a logistic regression model of hypertriglyceridemia was built using a stepwise procedure in the patients taking olanzapine, quetiapine, chlorpromazine or mirtazapine. The 9 ACACA SNPs, gender and long waist circumference were used as initial independent variables. The final model included as significant variables the SNPs rs2229416, rs12453407, rs7208415 and rs4795194, gender and waist circumference (p-values <0.05). The final model also included a borderline significant SNP (rs4794750; $p=0.06$). In contrast, when this model was fitted using the patients taking other antipsychotics, only long waist circumference was significant. This suggests that a number of the investigated ACACA SNPs may be somewhat independent signals from the *ACACA* gene, although ACACA SNPs may be closely interrelated. These results need to be replicated in

other samples. Unfortunately, the relationship between ACACA SNPs and the phenotype determined by the *ACACA* gene is unknown, and we do not know whether other SNPs that are more relevant for the phenotype exist.

An association between the *ACACA* gene and hypertriglyceridemia is consistent with the ACACA enzyme's role in fatty acid synthesis and with the potential use of this enzyme's inhibitors in metabolic syndrome treatments (Harwood, 2005). In vitro or animal studies are needed to verify the hypotheses that clozapine, olanzapine, quetiapine, chlorpromazine, and possibly mirtazapine, increase this enzyme's activity, and that other antipsychotics (i.e., antipsychotics with a chemical structure not comparable to that of the above antipsychotics) do not affect the enzyme.

4.2. Lack of association of additional NPY and ACACB SNPs with severe hypercholesterolemia

None of the 3 additional *NPY* SNPs or the 7 *ACACB* genes yielded significant results, which suggests that the initial significant results for NPY (rs1468271) and ACACB (rs2241220) may be false positives due to multiple testing. It is also possible that we did not select the appropriate SNPs for verifying the initial findings.

4.3. Limitations

This study has all the limitations of naturalistic, exploratory genetic studies, although potential confounders (especially obesity) were controlled. It was not possible to control for antipsychotic treatment duration. However, this cross-sectional study may have detected 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 may not have important direct effects on hyperlipidemia (de Leon and Diaz, 2007). Ideally, an expensive prospective design may be needed to control for treatment duration. To decrease the weakness of our data we have focused on the short-term effects that antipsychotics have on lipids, carefully controlling for obesity; and on the major effects by looking for obvious cases of hyperlipidemia and using very “tough” controls who were taking antipsychotics with limited or no effects on H1 blocking. The authors focused on study replication rather than correction for multiple testing (de Leon and Diaz, 2007; de Leon et al., 2008). Moreover, this article describes a third set of analyses of the same sample. These analyses progressively improved our understanding of the sample. Initially, the direct effects on lipid levels of some atypical antipsychotics were investigated (de Leon et al., 2007). Then, the direct effects of antipsychotics with H1 blocking properties on obvious hyperlipidemia cases were studied (de Leon et al., 2008). Finally, the current study explored the direct effects of drugs that block H1 receptors (some antipsychotics or mirtazapine) on obvious hyperlipidemia cases. We started with 384 SNPs from 215 genes; complex statistical analyses selected 8 SNPs from 8 genes; biological plausibility led us to narrow this number to 3 SNPs in 3 genes (de Leon et al, 2008). In this article, additional SNPs led us to suggest that only 1 gene (*ACACA*) may be of interest for hypertriglyceridemia cases. The other two non-replicated genes may be explained by multiple testing.

One of the most consistent findings concerning metabolic disorders has been the association between a 5-HT2C polymorphism and antipsychotic-induced weight gain (Arranz and de Leon, 2007). However, not all studies have verified this association (Popp et al., 2009).

5. Conclusions

This study contributes to the literature of antipsychotic pharmacogenetics and further supports the hypothesis that the direct effects of some antipsychotics on hypertriglyceridemia may be at least partially mediated by the *ACACA* gene. No support for the mediation of the *NPY* or *ACACB* genes on severe hypercholesterolemia was found.

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Contributors

Alexander Meary, M.D and Maria J. Arranz, Ph.D. selected the additional SNPs. Francisco J. Diaz, Ph.D., and Jose de Leon, M.D., designed the additional statistical analyses. Jose de Leon, M.D., designed the original study. Francisco J. Diaz, Ph.D., and 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 (since 9/21/06), Francisco J. Diaz, Ph.D. and Alexander Meary, M.D had no conflict of interest. In the past three years (since 9/21/06), Maria J. Arranz, Ph.D. has received consultancy money from TheraGenetics, LGC and Lundbeck. 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 NIH 2 R44 MH073291-02 “DNA Diagnostics for Minimizing Metabolic Side-Effects of Antipsychotics.” Currently, Jose de Leon, M.D., takes part in this NIH grant in collaboration with Genomas. In the last 3 years (since 9/21/06) he has lectured once supported by Eli Lilly and once by Roche Molecular Systems, Inc. He has never been a consultant for pharmaceutical or pharmacogenetic companies.

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