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Risperidone-Induced Weight Gain in Referred Children with Autism Spectrum Disorders Is Associated with a Common Polymorphism in the 5-Hydroxytryptamine 2C Receptor Gene

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Abstract

Weight gain is an important adverse effect of risperidone, but predictors of significant weight gain have yet to be identified in pediatric patients. Here, we investigated differences between age- and gender-normed body mass index–standardized *z* scores at baseline and after 8 weeks of open-label, flexible-dose risperidone treatment (mean dose: 1.70 mg/day) in 32 youths with pervasive developmental disorder (mean age = 8.74, range = 5–16 years) in relation to –759C/T 5-hydroxytryptamine 2C receptor (HTR2C) promoter and rs1414334 HTR2C intragenic C/G alleles, along with gender, age, and risperidone dose, using repeated measures analyses of variance. Carriers of the HTR2C promoter T allele gained an average of 0.043 ± 0.017 body mass index–standardized *z* scores (1.84 ± 1.51 kg) versus 0.64 ± 0.35 *z* (3.23 ± 1.47 kg) for non-T-allele carriers ($p < 0.001$). Presence of the rs1414334 C allele played no significant role. Further, weight gain appeared to be associated with younger age and higher doses of risperidone. The current preliminary findings suggest that the variant T allele of the –759C/T HTR2C promoter polymorphism is protective against risperidone-induced weight gain. Younger children and those treated with higher doses of risperidone may be at higher risk for weight gain.

Introduction

THE EFFICACY OF THE ANTIPSYCHOTIC agent risperidone in ameliorating disruptive and aggressive behavior is well established for children and adolescents with pervasive developmental disorder (Research Units on Pediatric Psychopharmacology Autism Network 2002; Troost et al. 2005) or intellectual disability (Findling et al. 2004). However, weight gain is an important adverse effect of risperidone, particularly for children (Safer 2004), mean gains being in the range of 2.2–2.8 kg in the first 8 weeks of treatment in controlled studies (Findling et al. 2004; Shea et al. 2004; Troost et al. 2005; Fleischaker et al. 2007). Weight gain has well-established health risks, which may include glucose dysre-

gulation, future cardiovascular disease, and development of the metabolic syndrome (Chia and Boston 2006); it may also have psychosocial consequences resulting from lowered self-esteem and social isolation (Puhl and Latner, 2007).

Although a pooled data analysis of available studies until mid-2003 suggested that younger children may be at a higher risk for weight gain when treated with risperidone (Safer 2004), determinants that increase or decrease the risk of risperidone-induced weight gain in pediatric patients have not been clearly established. For example, risperidone dose, concomitant medication use, age, pubertal status, gender, and baseline weight and body mass index (BMI) have not been predictive of weight gain in controlled studies (Hellings et al. 2001; Aman et al. 2005) and a retrospective chart

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review (Martin et al. 2004). A recent study, however, suggested that baseline BMI was negatively correlated with weight gain through long-term use of risperidone (Calarge et al. 2009). Thus far, the possible contribution of genetic factors to the susceptibility of weight gain in children treated with risperidone has not been evaluated.

Studies with adult patients have found evidence that genetic variation in the gene coding for the 5-hydroxytryptamine 2C (5HT_{2C}) receptor (HTR2C gene; located on the X chromosome at q24) is associated with interindividual differences in antipsychotic-induced weight gain (Reynolds et al. 2002). More precisely, presence of the variant T allele of the -759C/T polymorphism in the promoter region of the HTR2C gene (rs3813929) has been demonstrated to have protective effects against antipsychotic-induced weight gain. Moreover, a strong relationship between presence of the intragenic HTR2C rs1414334 C allele and the metabolic syndrome in adult patients using antipsychotic medication has been described by authors from our group (Mulder et al. 2007). Not all studies, however, have detected significant associations between HTR2C T/C polymorphisms and clozapine-induced weight gain (Park et al. 2008).

The association between risperidone-induced weight gain and HTR2C gene polymorphisms has not yet been examined in children and adolescents. We address this in the present study, in which we look at weight changes after 8 weeks of treatment with risperidone, in a flexible-dose, open label, prospective design. In addition to reporting absolute weight changes, we also use height and weight measures against appropriate age and gender normative values to calculate BMI-standardized *z* scores (Martin et al. 2000). This approach has the advantage of taking age and gender pediatric growth patterns into account.

Methods

Subjects

The sample consisted of 32 children (28 boys and 4 girls; mean age = 8.74, standard deviation [SD] = 2.83, range = 5–16 years) with a pervasive developmental disorder (based on clinical diagnosis with corroboration from the Autism Diagnostic Interview—Revised; Lord et al. 1994) who had participated in an open 6-month trial of risperidone followed by a placebo-controlled withdrawal (Troost et al. 2005). In addition to a diagnosis of pervasive developmental disorder, subjects also had serious behavioral problems such as tantrums, aggression, and/or self-injurious behavior. All participants were referred patients of either the Groningen or Utrecht University Child and Adolescent Psychiatry Center. The present study examined the effects of risperidone on weight and BMI in relation to HTR2C polymorphisms during the first 8 weeks of treatment. Of the 36 children who entered the trial, 32 subjects had a DNA sample taken for genotyping. Four of the 32 patients participated for < 8 weeks: one male patient discontinued after 5 weeks because of dystonia, another male patient after 7 weeks because of increased anxiety, and two girls stopped after 6 weeks for unknown reasons. We did not examine weight gains after 6 months of risperidone treatment, because only 22 of the 32 patients with available DNA completed the 6-month trial (i.e., only risperidone responders, as assessed after 8 weeks of treatment; Troost et al. 2005).

Prior to the study, ineffective medications were gradually withdrawn in a 7- to 28-day washout period. In the case of co-occurring attention-deficit/hyperactivity disorder, stimulants were allowed to be continued, provided no changes during the study

would occur; 8 of the 32 patients used stimulants, in all cases methylphenidate.

At study entry, children <45 kg of weight were given risperidone at an initial dose of 0.5 mg at bedtime, which was increased to 0.5 mg twice daily at day 7. The dose was gradually increased in 0.5 mg increments to a maximum of 2.5 mg/day by day 29. Children who weighed >45 kg could be prescribed slightly higher doses, with maximum daily doses of 3.5 mg by day 29. Dosing was flexible: clinicians were free to delay a scheduled increase or to reduce the medication dose depending on response or adverse events. At study end, mean daily dose of risperidone was 1.70 mg (SD = 0.78 mg, range = 0.50–3.50 mg).

The aim and study procedures were fully explained to the subjects and both parents before the parents' written consent was obtained, which included consent for genetic testing and permission to publish. If the subjects were 12 years or older, the written informed consent of the parents was obtained along with the patients' assent. The study was approved by the Dutch Central Review Board (The Hague, The Netherlands).

Genotyping

DNA was extracted from 80 μ L of ethylenediaminetetraacetic acid-anticoagulated whole blood with a Generation Capture Column Kit (Genra Systems, Minneapolis, MN) according to the manufacturer's instructions. We determined genotypes of rs3813929: C > T (-759C/T), in the promoter region of the X-linked HTR2C gene, and of rs1414334: C > G, an intragenic polymorphism in intron 5 close to the HTR2C 3' untranslated region. Genotyping was performed by pyrosequencing as described previously (Mulder et al. 2007). The genotyping results were blinded to the researcher and were not available to the treating psychiatrist before data analysis.

Data analysis

Possible differences in baseline BMI-standardized *z* scores, based on Dutch age- and gender-normed growth charts (available at <http://groeiweb.pgdata.nl>), between carriers and noncarriers of the rs3813929 T allele and the rs1414334 C allele, respectively, were evaluated with *t*-tests. Further, we performed repeated measures analysis of variance (ANOVA). In the first analysis, we only looked at pre- and posttreatment BMI-standardized *z* scores, but also report changes in body weight. This was followed by entering the presence of the rs3813929 T allele and the rs1414334 C allele, respectively, as between-subject factor, to assess crude effects of genotypes. Finally, we also added risperidone dose, age, gender, and concomitant use of methylphenidate as covariates. To rule out possible effects of baseline weight, we additionally did a repeated measures ANOVA on body weight between carriers and noncarriers of the rs3813929 T allele, with baseline weight as covariate. In subjects participating for <8 weeks, we used the last observation carried forward model. All tests were two-tailed and used *p*-values <0.05 to indicate statistical significance.

Results

Age- and gender-normed BMI-standardized *z* scores changed significantly (univariate repeated measures ANOVA: $F = 50.9$, degrees of freedom [df] = 31, $p < 0.001$) from baseline (mean standardized BMI = 0.53 *z*, SD = 1.27 *z*, range = -2.20–3.30 *z*) to posttreatment (mean standardized BMI = 1.03 *z*, SD = 1.26 *z*,

range = -1.40 – 3.50 z), corresponding to a mean weight gain of 2.9 kg. Standardized BMI scores increased in 28 children (range = 0.10 – 1.60 z), remained unchanged in 3 children, and decreased in 1 child (by 0.3 z). In absolute kg, all except one child (who experienced a weight loss of 0.3 kg) gained weight (range = 0.6 – 7.7 kg).

Seven of the 32 children (21.9%; 4 males and 3 females) carried the rs3813929 T allele; the rs1414334 C allele was present in 5 of the 32 children (15.6%; all males). There were no statistically significant differences in baseline BMI-standardized z scores or in absolute weight (t -test: $t = -0.60$, $df = 30$, $p = 0.66$; and $t = -1.67$, $df = 30$, $p = 0.11$, respectively) between carriers of the rs3813929 T allele (mean = 0.79 z , $SD = 1.37$ z , range = -0.60 – 3.30 z ; and mean = 45.4 kg, $SD = 29.4$ kg, range = 22.8 – 107.2 kg, respectively) and those who did not carry the allele (mean = 0.46 z , $SD = 1.27$ z , range = -2.20 – 3.00 z ; and mean = 33.2 kg, $SD = 12.1$ kg, range = 20.2 – 61.5 kg, respectively). Similarly, no such differences were present between carriers and noncarriers of the rs1414334 C allele. Entering the presence of the rs3813929 T allele as between-subject factor in the repeated measures ANOVA revealed a significant effect of this allele on risperidone-induced increases in BMI-standardized z scores ($F = 18.7$, $df = 30$, $p < 0.001$). Carriers of the rs3813929 T allele gained an average of 0.043 BMI-standardized z scores ($SD = 0.17$ z , range = -0.30 – 0.20 ; from a group mean of 0.79 to 0.83) versus 0.64 z ($SD = 0.35$ z , range = 0.00 – 1.60 z ; from 0.46 to 1.09 z) for noncarriers (Fig. 1). The weight gain in the group with the rs3813929 T allele was 1.84 ($SD = 1.51$ kg) compared with 3.23 ($SD = 1.47$ kg) for the noncarriers. In contrast, presence of the rs1414334 C allele played no significant role ($F = 2.08$, $df = 30$, $p = 0.16$). This reflects effect sizes (Cohen's d) of the rs3813929 T allele on increase in BMI-standardized z scores and weight gain of 2.16 and 0.93, respectively.

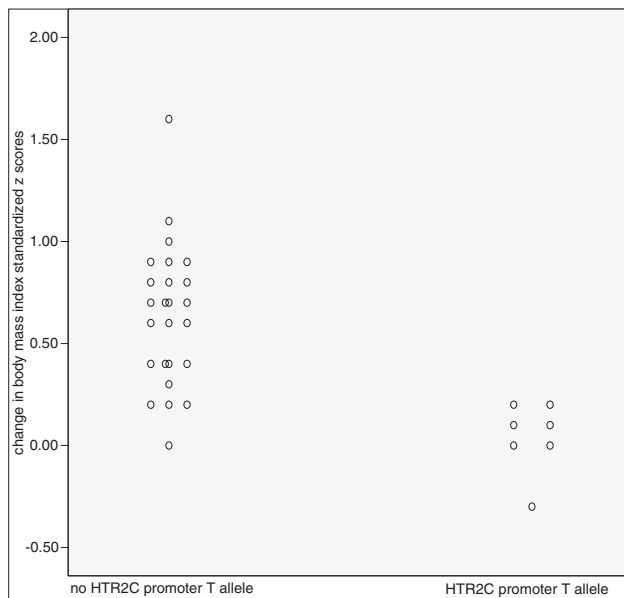


FIG. 1. Change in age- and gender-normed body mass index-standardized z scores after a 6-week open-label treatment with risperidone in seven carriers of the HTR2C promoter T allele (gaining an average of 0.043 ± 0.017 body mass index-standardized z scores) and 25 non-T-allele carriers (mean weight gain of 0.64 ± 0.35 z). HTR2C = 5-hydroxytryptamine 2C receptor gene.

TABLE 1. RESULTS OF REPEATED MEASURES ANALYSIS OF VARIANCE REGARDING CHANGE IN BODY MASS INDEX-STANDARDIZED Z SCORES IN 32 CHILDREN WITH A PERVERSIVE DEVELOPMENTAL DISORDER RECEIVING 8 WEEKS OF TREATMENT WITH RISPERIDONE

Possible determinants of weight gain ^a	Repeated measures statistics
Presence of rs3813929 T allele	$F = 8.18$, $df = 26$, $p = 0.008$
Gender	$F = 1.08$, $df = 26$, $p = 0.31$
Use of methylphenidate	$F = 0.030$, $df = 26$, $p = 0.86$
Age	$F = 6.21$, $df = 26$, $p = 0.019$
Risperidone dose	$F = 4.39$, $df = 26$, $p = 0.046$

^aBetween subject factors or covariates.
Abbreviation: df = degrees of freedom.

Table 1 shows the results of a repeated measures ANOVA regarding the number of possible determinants of risperidone-induced gain in BMI-standardized z scores. Gender (n of girls = 4) and the concomitant use of methylphenidate ($n = 8$) were not associated with risperidone-induced weight gain. Gain in BMI-standardized z scores appeared to be associated with younger age and higher doses of risperidone: children below the median age of 8.26 years gained an average of 0.63 BMI-standardized z scores versus 0.38 z for children above 8.26 years (mean weight gain was 3.0 and 2.9 kg, respectively). Children receiving less than the median level risperidone (i.e., 1.5 mg/day) gained an average of 0.38 z BMI versus 0.57 z for children receiving 1.5 mg/day or more (average weight gain was 2.6 and 3.1 kg, respectively). Mean risperidone doses in mg/kg/day were similar in children below (0.053 mg/kg/day) and above (0.047 mg/kg/day) the median age.

Finally, a repeated measures ANOVA on body weight between carriers and noncarriers of the rs3813929 T allele, with baseline weight as covariate, confirmed the significant effect of the T allele ($F = 8.61$, $df = 30$, $p = 0.006$).

Discussion

The main finding of our study is that children and adolescents with the variant $-759T$ allele in the promoter of the HTR2C gene are protected against risperidone-induced weight gain. In children without this variant, 8 weeks of flexible-dose use of risperidone was associated with an age- and gender-normed mean increase of 0.64 BMI-standardized z scores (absolute mean weight gain of 3.23 kg) versus little or no (i.e., 0.043 standardized z scores; mean weight gain of 1.81 kg) increase in carriers of the $-759T$ allele. Although findings with clozapine have been somewhat inconsistent (Basile et al. 2002; Reynolds et al. 2002; Tsai et al. 2002; Theisen et al. 2004), these results are in line with the protective effect of the variant T allele against antipsychotic-induced weight gain in several studies of adults with schizophrenia (Ellingrod et al. 2005; Templeman et al. 2005; Lane et al. 2006; Ryu et al. 2007).

Risperidone acts as an antagonist against HTR2C (Canton et al. 1994). There is ample evidence that the HTR2C is directly involved in weight regulation, probably through appetite control (Somerville et al. 2007). The $-759T$ HTR2C promoter allele shows higher transcription levels of the HTR2C gene than the $-759C$ allele (Buckland et al. 2005) and has been found to be more common in obese than in nonobese women (Pooley et al. 2004). Interestingly, 5HTR2C knockout mice are prone to increased feeding and obesity

(Tecott et al. 1995; Memon et al. 2000). Moreover, agonists of the HTR2C have been shown to decrease weight and food intake in rats (Luo and Li 1991; Rosenzweig-Lipson et al. 2006), mice (Somerville et al. 2007), and humans (Sargent et al. 1997; Nilsson 2006). Further, in animal studies, it has been demonstrated that antipsychotics downregulate HTR2C mRNA (Buckland et al. 1997). It is conceivable that high baseline expression levels of HTR2C, as in $-759T$ carriers, may tend to mitigate antagonistic and down-regulatory effects of risperidone at the receptor.

Apart from the influence of the $-759C/T$ polymorphism, higher risperidone dose and younger age appeared to be positively associated with weight gain in our study. Although Martin et al. (2004) did not observe an association between risperidone dose and weight gain in the Research Units on Pediatric Psychopharmacology (RUPP) Autism Network study, a clear dosing effect has been identified in adult studies (Lane et al. 2003; Theisen et al. 2004). It should be noted that risperidone doses in the present study, prescribed for behavior problems, have been lower than those typically used in the treatment of psychoses. A pooled data analysis based on available double-blind and open trials, as well as case series, also had shown that risperidone-induced weight gain is most pronounced in the preadolescent years and decreases with advancing age (Safer 2004). In the RUPP study, however, younger age was not associated with weight gain (Martin et al. 2004). Martin et al. (2004) did note that weight gain was most rapid in the first 2 months of treatment. Thus, the fact that the RUPP study investigated weight change after 6 months of risperidone treatment and our study looked at effects after 2 months of treatment may be an important difference. Moreover, our study included eight children (25% of study participants) on methylphenidate, whereas the RUPP study did not allow treatment with another medication.

Our study has clear clinical implications. It provides additional confirmation that weight gain is a frequent and important adverse effect of risperidone in children. Younger children and those using higher doses may be at increased risk of weight gain. However, the results also indicate that this adverse effect is unlikely to occur in a substantial proportion of children (those with the $-759T$ allele). Given the physiological and psychosocial consequences of atypical antipsychotic-induced weight gain, genotyping the HTR2C promoter $-759C/T$ polymorphism may become a standard clinical practice when considering treating children with such agents.

In conclusion, the small sample size is acknowledged as an important limitation of the present study that underlines the preliminary character of our study findings, specifically given the combination of the low number of patients and the uneven distribution of genotypes. Moreover, all patients had an autism spectrum disorder and the far majority of patients were boys, limiting the generalizability of our findings. Therefore, it is clear that replication is required. However, the use of BMI-standardized z scores, rather than absolute weight, made the groups similar in terms of variance, and thus the results of statistical testing more sensitive. Still, the limited study power may be one explanation for the lack of effect of the rs1414334 C allele. This and other candidate polymorphisms possibly associated with risperidone-induced weight gain (such as adrenergic $\alpha 2a$ receptor genes, the gene for leptin guanine nucleotide binding protein, and the gene for synaptosomal-associated protein [25 kDa]; Muller and Kennedy 2006) should be examined along with the $-759C/T$ polymorphism in future studies (with larger samples sizes) of antipsychotic-induced weight gain in children. Future studies could also investigate the effectiveness of weight gain prevention programs in children treated with antipsychotic medications.

Disclosures

Dr. P.J. Hoekstra has been a paid consultant to Desitin and Eli Lilly; Dr. J.K. Buitelaar is a paid consultant to or has received support from Janssen Cilag, Abbott, VCB, Shire, Medice, and Eli Lilly; Dr. R.B. Minderaa is a paid consultant to Eli Lilly and Janssen Cilag; Dr. L. Scahill is a paid consultant to Janssen Pharmaceutica, Inc., Bristol-Myers Squibb, and Pfizer; Dr. P.W. Troost has received support from Eli Lilly. The other authors have no financial relationships to disclose. However, data have been analyzed and the article was written by the primary author.

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