ORIGINAL ARTICLE

The Role of Serotonin Transporter Protein Gene in Antidepressant-Induced Mania in Bipolar Disorder

Preliminary Findings

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Background: The occurrence of mania during antidepressant treatment is a key issue in the clinical management of bipolar disorder (BP). The serotonin transporter (5-HTT) is the selective site of action of most proserotonergic compounds used to treat bipolar depression. The 5-HTT gene (*SLC6A4*) has 2 known polymorphisms. The aim of this study was to investigate the role of the *SLC6A4* variants in the pathogenesis of antidepressant-induced mania in BP.

Methods: Twenty-seven patients with a *DSM-IV* diagnosis of BP I or II, with at least 1 manic or hypomanic episode induced by treatment with proserotonergic antidepressants (IM+ group), were compared with 29 unrelated, matched patients with a diagnosis of BP I or II, who had been exposed to proserotonergic antidepressants without development of manic or hypomanic symptoms (IM– group). The 2 known polymorphisms of the *SLC6A4* were genotyped, and allelic and genotypic association analyses were performed.

Results: With respect to the polymorphism in the promoter region (*5HTTLPR*), IM+ patients had an excess of the short allele (n=34 [63%]) compared with IM– patients (n=17 [29%]) (χ^2_1, 12.77; $P < .001$). The genotypic association analysis showed a higher rate of homozygosity for the short variant in the IM+ group (n=10 [37%]) than in the IM– group (n=2 [7%]) and a lower rate of homozygosity for the long variant in the IM+ group (n=3 [11%]) compared with the IM– group (n=14 [48%]) (χ^2_2, 12.43; $P=.002$). No associations were found for the polymorphism involving a variable number of tandem repeats.

Conclusion: If these results are replicated, the *5HTTLPR* polymorphism may become an important predictor of abnormal response to medication in patients with BP.

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THE INDUCTION of mania in patients treated with antidepressants is a complex and not rare phenomenon that occurs with different frequencies in patients with bipolar disorder (BP), unipolar disorder (UP), and obsessive-compulsive disorder.[1-8] In patients with mood disorder, the frequency of antidepressant-induced mania has been estimated to be 9.5% to 33%, varying across studies that included different diagnoses (ie, UP and BP) and different antidepressant treatments.[9-11] More recently, it has become clearer that the phenomenon of antidepressant-induced mania was strictly related to a diagnosis of BP, and that, in these patients, the switch rate during antidepressant treatment was definitively higher than that in patients with UP.[12] Therefore, during the 1990s, researchers have primarily focused on the occurrence of the phenomenon in BP.

Whether the type of antidepressant treatment can influence the risk for mood switches remains controversial. According to Solomon et al,[2] a manic switch during antidepressant treatment occurs in approximately 20% of the BP inpatient admissions, regardless of treatment (tricyclic antidepressants, monoamine oxidase inhibitors, or electroconvulsive therapy). On the other hand, some reports showed that the rate of induction of mania is higher in patients with BP who are treated with tricyclic antidepressants and monoamine oxidase inhibitors than in patients with BP who are treated with selective serotonin reuptake inhibitors (SSRIs).[8,13]

As the impact on the clinical management of BP created by the occurrence of antidepressant-induced manic switches is quite high,[1,14] several studies have focused on the possible clinical predictors and features of this phenomenon. A higher number of previous manic or hypomanic episodes appeared to be the only clinical variable affecting the risk for development of mania during antidepressant treat-

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SUBJECTS AND METHODS

SUBJECTS

The subjects undergoing investigation for the purpose of this study have been selected from a larger sample of 300 patients with BP I or BP II recruited from hospital clinics and newspaper advertisements in Toronto, Ontario, and across central Canada, within the research protocols of our group. All of these patients had been administered the Diagnostic Structured Interview for *DSM-IV* Axis I diagnoses (SCID-I)[34] and the Family Interview for Genetic Studies (FIGS)[35] by trained interviewers. From all patients and their parents, we obtained written informed consent to participate in the genetic studies ongoing in our research group, which also included the use of personal and clinical data and blood drawing for genotyping.

The SCID-I, the FIGS, the clinical and life charts available, and all information about past and current pharmacological treatment recorded during the interviews were blindly and independently reviewed by 2 trained psychiatrists (E.M. and J.L.K.). Considering the retrospective nature of this study, to avoid investigators' biases, only information and life charts that existed before the design of the present investigation have been used.

Based on this review, from the original sample of 300 patients with BP I and BP II, we were able to select 2 groups of unrelated patients. The first group consisted of 27 subjects with a positive history for antidepressant-induced mania (IM+ group). It included patients with the following characteristics: (1) a confirmed *DSM-IV* diagnosis of BP I or BP II, (2) at least 1 depressive episode treated with proserotonergic antidepressants, and (3) at least 1 manic or hypomanic episode induced by treatment with these compounds (ie, 1 episode fulfilling *DSM-IV* criteria for mania or hypomania, which developed during antidepressant treatment). The second group, without the history of antidepressant-induced mania (IM– group), consisted of 29 patients with the following characteristics: (1) a confirmed diagnosis of BP I or BP II, (2) at least 1 depressive episode treated with proserotonergic antidepressants, and (3) no antidepressant-induced manic or hypomanic episodes.

Patients within the IM– group were matched by sex, age (± 5 years), and ethnicity (including preimmigration roots) with the patients of the IM + group. The matching procedure we used implied the possibility of using more than 1 control subject per case subject, when available.

We excluded subjects with (1) uncertain *DSM-IV* diagnosis of BP (including patients with only 1 manic or hypomanic episode induced by antidepressant treatment and no spontaneous ones, for whom there is to date no consensus about the diagnosis of BP); and/or (2) unavailable, inadequate, or unreliable information on past and current psychopharmacological treatments (eg, report of exposure to antidepressant treatment but no information about the type of antidepressant); and/or (3) no history of exposure to proserotonergic antidepressants.

For IM+ and IM– groups, we collected the following demographic and clinical variables from the SCID-I and the FIGS: age at time of the interview, age at onset of BP, diagnostic subtype of BP, comorbid Axis I diagnoses, family history of mood disorders, number of spontaneous manic or hypomanic episodes, number of depressive episodes, presence or absence of psychotic symptoms during the mood episodes, presence or absence of rapid cycling, and presence or absence of suicidal behavior. Information about

ment.[8,12] Stoll et al[15] reported that antidepressant-induced manic or hypomanic episodes are clinically different from spontaneous ones, having a shorter duration and less severe psychotic symptoms.[15]

The serotonin transporter (5-HTT) is the selective site of action of several antidepressants commonly used to treat bipolar depression.[16] Bipolar disorder has been shown to have a strong genetic component,[17-19] and thus, the 5-HTT protein gene (*SLC6A4*) has been considered an ideal candidate for the investigation of the genetic component of BP and the response to antidepressant medication.

The *SLC6A4* is located on chromosome 17 and has 2 common polymorphisms. One is in the promoter region (*5HTTLPR*), consisting of a 44–base pair (bp) insertion or deletion.[20] The long variant (*l*) has been reported to generate more gene expression than the short one (*s*).[20]

Investigation into the involvement of the *5HTTLPR* polymorphism in the pathogenesis of BP has led to conflicting results. Among the several case-control association studies performed, only 2 studies detected a positive association between the *s* variant of the gene and BP,[21,22] whereas 2 recent linkage studies yielded negative findings.[23,24] The other polymorphism in the *SLC6A4* consists of a variable number of tandem repeats (*VNTR*) in the second intron, with 3 alleles (*STin2*9*, *STin2*10*, and *STin2*12*).[25] Recent studies appear to exclude any associations between this polymorphism and BP.[26-29]

With respect to the role of the *5HTTLPR* polymorphism in antidepressant response, patients with major depression who are homozygous or heterozygous for the *l* variant appear to show a better response to fluvoxamine maleate[30] and paroxetine.[31] Patients with bipolar depression who are homozygous for the *l* variant of the *5HTTLPR* polymorphism have been found to have a better clinical response to total sleep deprivation.[32]

To date, there are no studies on the involvement of the *5HTTLPR* polymorphism in the induction of mania during antidepressant treatment, but a recent report from a pilot investigation suggested an association with the *s* variant.[33] The aim of the present study was to investigate further the role of the 5HTT protein gene in the pathogenesis of manic or hypomanic switches in patients with BP treated with proserotonergic agents.

RESULTS

The main demographic (including ethnic background) and clinical variables for both patient groups are summarized in **Table 1**. No significant differences were found between groups for the variables considered.

Data regarding past or current treatment with mood stabilizers (lithium carbonate, carbamazepine, or valproate sodium) were available for 50 patients, 23 in the IM+ group and 27 in the IM– group. In the IM+ group, infor-

current or past treatment with mood stabilizers was also recorded from the clinical charts, where available.

GENOTYPING

Genomic DNA was extracted from blood samples using a nonenzymatic procedure.[36] All genotyping procedures have been performed without the researchers aware of the aim and design of this study and the clinical diagnoses of the subjects investigated.

SLC6A4 PROMOTER REGION

Polymerase chain reaction (PCR) was used to amplify a segment of genomic DNA containing the insertion or deletion polymorphism in the promoter region of the *SLC6A4* using primers with the sequences reported by Cook et al.[37] The PCR was performed in a 25-µL volume containing 200 ng of genomic DNA; 10-mmol/L Tris hydrochloride; 50-mmol/L potassium chloride; 1.5-mmol/L magnesium dichloride; 5% dimethyl sulfoxide; 200 µmol/L each of deoxyadenosine triphosphate (dATP), deoxythymine triphosphate (dTTP), and deoxycytosine triphosphate (dCTP); 100 µmol/L of deoxyguanosine triphosphate (dGTP); 100 µmol/L of 7-deaza-dGTP; 1 µmol/L of each primer; and 1 U of Ampli*Taq* DNA polymerase (Applied Biosystems Inc, Foster City, Calif). The genomic DNA was denatured at 95°C for 3 minutes, then the remaining reaction components were added. The reaction consisted of 40 cycles of 95°C for 30 seconds, 61°C for 30 seconds, and 71°C for 60 seconds, followed by extension at 72°C for 10 minutes. The PCR products were visualized on a 2.5% agarose gel and visualized under UV light in the presence of ethidium bromide. The DNA bands were assigned allele numbers based on their size (allele 1 [*l*], 450 bp; allele 2 [*s*], 406 bp).

SLC6A4 VARIABLE NUMBER OF TANDEM REPEATS

The 25-µL reaction modified from that of Cook et al[37] consisted of 200 ng of template; 0.8 µmol/L of each primer; 10-mmol/L Tris hydrochloride; 50-mmol/L potassium chloride; 1-mmol/L magnesium dichloride; 200 µmol/L each of dATP, dCTP, and dTTP; 150-µmol/L dGTP; 50-µmol/L 7-deaza-dGTP; 8% dimethyl sulfoxide; and 1 U of Ampli-*Taq* DNA polymerase (Applied Biosystems Inc). Cycling conditions consisted of initial denaturation for 3 minutes at 95°C, followed by 40 cycles of 45-second denaturation at 95°C, 30-second annealing at 56°C, and a 45-second extension at 72°C, ending with a final 7-minute extension at 72°C. After separation on a 2.5% agarose gel for 2 hours at 100 V, the 3 alleles produced bands at 345 bp (9 repeats), 360 bp (10 repeats), and 390 bp (12 repeats).

STATISTICAL ANALYSIS

All demographic and clinical variables available were tabulated and compared between both samples of patients studied. The *t* test (2-tailed) for independent samples was used for the continuous variables, whereas the χ^2 test was used for the dichotomous ones.

The genotype data for both polymorphisms were analyzed using Pearson χ^2 tests. Allele and genotype frequencies were compared between the IM+ and IM– groups. The α level of significance used was set at .05, and was not adjusted. All the statistical analyses were performed using commercially available software (SPSS for Windows, version 10.1; SPSS Inc, Chicago, Ill).

mation was available for 10 patients regarding the time of the induction of mania during the exposure to antidepressants: 5 were receiving mood stabilizers, and 5 were not. In the IM– group, 20 patients were receiving mood stabilizers at the time of the exposure to the antidepressant treatment (when mania did not develop), and 13 of them had spontaneous manic episodes while receiving mood stabilizers. Reliable data on daily doses and plasma levels at the time of the exposure to the antidepressants were available for only a few patients and thus, also considering that these variables were not standardized, no analysis was performed.

In the IM+ group, the ongoing antidepressant treatments during the development of manic or hypomanic episodes included fluoxetine hydrochloride (n=8), fluvoxamine (n=6), a combination of fluoxetine and fluvoxamine (n=3), paroxetine (n=2), nefazodone hydrochloride (n=2), moclobemide (n=2), venlafaxine hydrochloride (n=1), imipramine hydrochloride (n=2), and sertraline hydrochloride (n=1). Reliable data on daily doses and treatment duration at the time of the induction of mania were not available.

Genotypes and allele frequencies for the 2 polymorphisms studied in the total sample and in the IM+ and IM– groups are shown in **Table 2**.

The whole sample and both subsamples defined by the diagnosis were within the equilibrium of the Hardy-Weinberg law for both polymorphisms studied.

Results of the association analysis performed with the alleles and genotypes of the *VNTR* polymorphism did not show any significant difference between the patient groups. On the other hand, with respect to the *5HTTLPR* polymorphism, the allelic association analysis showed that among IM+ patients, there was an excess of the *s* allele (Pearson χ^2_1, 12.77; $P < .001$). The association analysis performed with the genotypes was also significant, showing a higher rate of homozygosity for the *s* variant and a lower rate of homozygosity for the *l* variant among IM+ patients (Pearson χ^2_2, 12.43; $P=.002$).

The odds ratio associated with the presence of the *s* variant was 4.1 (95% confidence interval, 1.84-8.65) (Table 2). Given a disease allele frequency of approximately 60% and a genotype relative risk of 2, with our sample it is possible to detect a significant allelic effect with a power ranging from 0.65 to 0.96 at $\alpha=.05$, depending on the expected effect size.

COMMENT

The main finding from this study suggests a role for the *s* variant of the *5HTTLPR* polymorphism in conferring a higher risk for development of antidepressant-induced mania in patients with BP treated with proserotonergic

Table 1. Demographic and Clinical Variables in Patients With and Without Antidepressant-Induced Manic/Hypomanic Episodes*

	IM+ Group (n = 27)	IM– Group (n = 29)
Sex, M/F	9:18	9:20
Ethnicity, No. (%)		
White	26 (96)	28 (97)
East Asian	1 (4)	1 (3)
Age, mean (SD), y	36.3 (8.5)	36.3 (7.7)
Age at onset, mean (SD), y	19.8 (5.5)	19.5 (6.2)
Principal Axis I Diagnosis, No. (%)		
Bipolar I	15 (56)	19 (66)
Bipolar II	12 (44)	10 (34)
Axis I comorbidity, No. (%)†		
None	12 (44)	16 (55)
Obsessive-compulsive disorder	6 (22)	3 (10)
Panic disorder	5 (19)	5 (17)
Social phobia	3 (11)	1 (3)
Simple phobia	0	1 (3)
Alcohol abuse/dependence	2 (7)	1 (3)
Substance abuse/dependence	1 (4)	1 (3)
Posttraumatic stress disorder	1 (4)	2 (7)
Generalized anxiety disorder	0	1 (3)
Family history for mood disorders, No.‡		
Negative	5	9
Bipolar disorder	12	11
Major depressive disorder	9	6
No. of depressive episodes, mean (SD)	5.9 (4.6)	4.5 (2.4)
No. of manic/hypomanic episodes, mean (SD)	3.8 (1.8)	3.7 (2.1)
Psychotic features, No. (%)	19 (70)	15 (52)
Rapid cycling, No. (%)§	3 (11)	2 (7)
Suicidal behavior, No.‖		
Suicidal plans	3	6
Suicidal attempts	2	3

*IM+ indicates patients with antidepressant-induced manic/hypomanic episodes; IM–, patients without these episodes.

†The total exceeds 100% because of multiple diagnoses.

‡Data were not available for 4 patients.

§Includes number of patients with at least 4 episodes of mood disturbance in the previous 12 months meeting DSM-IV criteria for major depressive, mixed, manic, or hypomanic episode.

‖Includes number of patients with suicidal behavior (lifetime). Data were not available for 4 patients.

compounds. This result appears to confirm a previous finding from a pilot investigation, in which the genotype and allele frequencies for the *5HTTLPR* polymorphism were compared between a smaller sample of patients with BP and antidepressant-induced manic or hypomanic episodes and a larger group of unmatched patients with BP and only spontaneous episodes.[33]

We hypothesized that patients with BP who are homozygous for the *s* variant, having lower gene expression and, thus, fewer 5-HTT sites, could be more sensitive to the block of serotonin reuptake or to the increase of serotinin availability. A lower number of 5-HTT sites would imply higher levels of serotonin in the synaptic cleft as a consequence of a lower reuptake rate. Thus, these subjects would be more likely to exhibit an enhanced response to compounds that block serotonin reuptake and increase further synaptic serotonin levels. Both effects were induced in our IM+ sample during treatment with SSRIs, imipramine, nefazodone, venlafaxine, or moclobemide. These compounds act directly or indirectly on serotonin neurotransmission,[16,38,39] and thus can be referred to as proserotonergic antidepressants.

If our hypothesis is true, and if the induction of mania represents only an exaggeration of the expected response to antidepressants, patients with the *ss* genotype should be more likely to respond to proserotonergic antidepressants or to show a shorter latency for the response. On the contrary, the *s* variant of the *5HTTLPR* polymorphism has been associated with poor response to SSRIs[30,31] or to total sleep deprivation.[32] However, the relationship between the *5HTTLPR* polymorphism and the expected antidepressant response remains controversial, considering that a recent report[40] associates good response to SSRIs with the *ss* genotype. It is quite likely that the lack of homogeneity across these different studies, with respect to the diagnosis (BP or UP), the compounds administered, or the definition of the antidepressant response, have been reflected in discordant results. In addition, the involvement of targets other than the 5-HTT in the response to proserotonergic compounds is quite likely. The critical role of serotonin presynaptic autoreceptors (ie, serotonin$_{1A}$) in determining the timing and the extent of the antidepressant response to medication has been pointed out[16] and discussed with respect to the recent associations between the *SLC6A4* variants and the response to SSRIs.[41]

Several limitations of this study should be considered. Whether antidepressant-induced manic switches in BP are phenomena quantitatively or qualitatively different from the expected antidepressant response is still unclear. The natural course of BP is characterized by the spontaneous recurrence of episodes of depression and mania or hypomania, and this could be a confounding factor in the detection of the rates and of the predisposing factors to antidepressant-induced phenomena, such as manic or hypomanic switches and rapid cycling courses. As stated by Coryell et al,[42] in BP, the occurrence of a major depressive episode may naturally anticipate a switch and, at the same time, may induce treatment with antidepressants, leading to an apparent, but not true, causal connection between the two events. Thus, the phenomenon of antidepressant-induced mania should be defined and investigated with controlled prospective studies in which all clinical and pharmacological variables known to be predictive factors are controlled a priori. Our study was performed according to a retrospective design, and although the review of the clinical information and the genotyping have been performed blindly, the lack of a prospective design represents a limitation. The doses and the treatment duration for the proserotonergic antidepressants administered were not controlled for in this study, and the information available did not allow us to verify whether these variables were comparable between IM+ and IM– patients. On the other hand, to our knowledge, there are no studies showing that antidepressant-induced manic or hypomanic episodes are related to these variables. According to the information extracted from the sample, there were no differences between IM+ and IM– groups with respect to the pharmacological variable that would have the most

Table 2. Genotype and Allele Frequencies for the Polymorphisms of the Serotonin Transporter Gene in Both Groups of Patients*

Polymorphisms	Total Sample (N = 56)	IM+ Group (n = 27)	IM– Group (n = 29)	χ^2 (*df*)	2-Sided *P*
5HTTLPR					
Alleles					
l	61 (54.5)	20 (37.0)	41 (70.7)	12.770 (1)	<.001†
s	51 (45.5)	34 (63.0)	17 (29.3)		
Genotypes					
ll	17 (30.4)	3 (11.1)	14 (48.3)	12.432 (2)	.002‡
ls	27 (48.2)	14 (51.9)	13 (44.8)		
ss	12 (21.4)	10 (37.0)	2 (6.9)		
VNTR§					
Alleles					
*STin2*9*	2 (1.9)	2 (4.0)	0	4.910 (2)	.09
*STin2*10*	35 (32.4)	12 (24.0)	23 (39.7)		
*STin2*12*	71 (65.7)	36 (72.0)	35 (60.3)		
Genotypes					
*STin2*9/STin2*10*	1 (1.9)	1 (4.0)	0	5.420 (4)	.25
*STin2*9/STin2*12*	1 (1.9)	1 (4.0)	0		
*STin2*10/STin2*10*	5 (9.3)	1 (4.0)	4 (13.8)		
*STin2*10/STin2*12*	24 (44.4)	9 (36.0)	15 (51.7)		
*STin2*12/STin2*12*	23 (42.6)	13 (52)	10 (34.5)		

**Data are given as number (percentage) of patients. Percentages have been rounded and may not sum 100. IM+ indicates patients with antidepressant-induced manic/hypomanic episodes; IM–, patients without these episodes;* 5HTTLPR*, polymorphism in the promoter region of the serotonin transporter protein gene; and* VNTR*, variable number of tandem repeats polymorphism.*

†*Likelihood ratio was 13.01 (*df *= 1);* P*<.001 (2-sided); Fisher exact test,* P *= .001 (2-sided). Odds ratio associated with the presence of the* s *variant was 4.1 (95% confidence interval, 1.84-8.65).*

‡*Likelihood ratio was 13.51 (*df *= 2);* P *= .001 (2-sided).*

§VNTR *genotyping was missing in 2 patients of the IM+ group; thus the percentages in this group have been computed on a total of 25 patients.*

significant impact on the risk for development of manic switches during the antidepressant treatment, ie, the concomitant treatment with mood stabilizers. Unfortunately, given that reliable information was not available for all patients, data could only be reported and commented on descriptively. Nonetheless, even though the percentage of patients in the IM– group receiving mood stabilizers at the time of the exposure to antidepressant treatment was higher than that in the IM+ group, spontaneous manic or hypomanic episodes developed in most of the IM– patients.

Ideal study designs would imply the exposure of drug-naïve patients with BP to antidepressants and mood stabilizers randomly and blindly, but these studies have obvious ethical and practical limitations. This is the main reason why the investigations of predictors and clinical characteristics of antidepressant-induced mania have been performed according to retrospective or naturalistic designs.[8,12,15]

Finally, it could be argued that the *s* allele of the *5HTTLPR* polymorphism might be associated primarily with clinical characteristics other than antidepressant-induced manic switches that confer severity to the illness and predispose patients to development of mania when exposed to antidepressants. In our sample, we did not find statistically significant differences in any of the clinical variables compared between IM+ and IM– patients. These included the presence of suicidal behaviors that have been associated with the presence of the *s* variant of the *5HTTLPR* polymorphism.[43] However, given the complexity of the clinical picture of BP, further studies on the predictive role of genetic factors in antidepressant-induced mania should consider matching patients for clinical variables that affect illness severity.

CONCLUSIONS

Despite the limitations, including small size of the samples studied, our study suggests a role of the *5HTTLPR* polymorphism in the pathogenesis of antidepressant-induced mania in BP. Further investigations are needed to confirm this result and to build comprehensive explanatory hypotheses for the complex mechanisms involved in determining the normal and the abnormal clinical responses to antidepressants.

If these preliminary results are confirmed in additional samples, the *5HTTLPR* polymorphism may become an important predictor of antidepressant-induced manic switches, which are among the most clinically damaging adverse effects of antidepressant treatment in patients with BP.

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