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Higher 5-HT_{1A} Receptor Binding Potential During a Major Depressive Episode Predicts Poor Treatment Response: Preliminary Data from a Naturalistic Study

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Serotonin 1A (5-HT_{1A}) binding potential (BP) as assessed by positron emission tomography (PET) is higher in major depressive disorder (MDD) in association with the higher expressing GG genotype of the 5-HT_{1A} C-1019G polymorphism. We hypothesize that higher 5-HT_{1A} BP and the GG genotype predict remission failure on antidepressant treatment. We determined 5-HT_{1A} BP by PET and 5-HT_{1A} C-1019G genotype in 43 controls and 22 medication-free MDD subjects. MDD was treated naturalistically and remission was defined as $>50\%$ reduction and a score of $\leqslant 10$ on the 24 item Hamilton Scale 1 year after initiation of treatment after scanning. Despite equivalent treatment, nonremitters have higher pretreatment cortical BP and the GG genotype is over-represented compared with remitters. Higher 5-HT_{1A} BP, perhaps due to greater gene expression, may predict antidepressant medication nonremission. The findings should be tested in a controlled prospective treatment study.
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INTRODUCTION

An association between the functional C-1019G promoter polymorphism of the 5-HT_{1A} gene and major depressive disorder (MDD) has been reported; MDD subjects are more likely to be homozygous for the GG genotype (Lemonde *et al*, 2003). The authors show that the C(-1019) allele is part of a 26 bp imperfect palindrome that binds the nuclear deformed epidermal autoregulatory factor (NUDR) transcriptional repressor, resulting in increased expression of the 5-HT_{1A} protein in the raphe nuclei (RN). Antidepressant naïve (AN) MDD subjects in a major depressive episode (MDE) exhibit higher 5-HT_{1A} binding potential (BP) in several brain regions when compared with controls as assessed *in vivo* using the positron emission tomography (PET) radioligand, [^{11}C]WAY-100635 (Parsey *et al*, in press). Further, GG depressed subjects are more likely to have higher 5-HT_{1A} BP (Parsey *et al*, in press). A poorer response to antidepressant treatment appears to be associated with the higher expressing GG genotype (Albert, 2004; Lemonde *et al*, 2004; Serretti *et al*, 2004).

We investigated the role of the 5-HT_{1A} receptor and C-1019G promoter polymorphism in predicting antidepressant treatment outcome by analyzing 1 year follow-up data from our previous PET study (Parsey *et al*, in press) using [^{11}C]WAY-100635 in 22 drug-free subjects with MDD who met criteria for a MDE and 43 healthy volunteers (controls). We hypothesized that MDD subjects exposed to community-based treatment and not in remission after 1 year would have higher 5-HT_{1A} BP and be more likely to have the higher expressing GG genotype compared with remitters.

MATERIALS AND METHODS

Subjects

In total, 22 subjects who met DSM-IV (APA, 1994) criteria for MDD and MDE and 43 controls were included in this study. Inclusion criteria was assessed through history, chart review, Structured Clinical Interview for DSM IV (SCID I) (First *et al*, 1995), Hamilton Depression Rating Scale (HAM-D) (Hamilton, 1960), review of systems, physical

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examination, routine blood tests, pregnancy test, urine toxicology, and EKG and are described elsewhere (Parsey *et al*, in press). Lifetime history of aggression was measured by the Brown Goodwin Aggression History Scale (Brown *et al*, 1979). Outcome assessments of 1 year included a clinical interview and the 24-item HAM-D. In total, 28 subjects were scanned at baseline and their data presented in a previous publication (Parsey *et al*, in press). Six of these depressed subjects did not receive 1-year post-treatment ratings; five were lost to follow-up and one missed the 1-year follow-up. Remission was defined as at least a 50% decrease from HAM-D 24 baseline score *and* a score of $\leqslant 10$ at the 1-year assessment (Bschor *et al*, 2002; Bschor *et al*, 2003; Keller, 2004; Lin *et al*, 1998; Paykel *et al*, 1995; Roose and Suthers, 1998; Smith *et al*, 2002). All subjects were treated with antidepressant medications during the year. In all, 14 of 22 were on medications at 1 year. A computerized version of the Antidepressant Treatment History Form (ATHF) was used to assess the adequacy of treatment during the year following the baseline PET scan (Oquendo *et al*, 2003; Sackeim *et al*, 1990). All subjects were medication-free for at least 2 weeks. The Institutional Review Boards of Columbia University New York Presbyterian Hospital and the New York State Psychiatric Institute approved the protocol. Subjects gave written informed consent after an explanation of the study and were treated in accordance with the Declaration of Helsinki.

Radiochemistry and Input Function Measurement

[^{11}C]WAY-100635 synthesis, measurement of the arterial input function and metabolites, and determination of the plasma free fraction (f_1) are described elsewhere (Parsey *et al*, 2005).

Image Analysis

Acquisitions of MRI and PET data and image analysis were performed as described elsewhere (Parsey *et al*, 2005). Briefly, dynamic PET images were acquired over 110 min following a 10 min transmission scan and were coregistered to the MRI. Irregular regions of interest (ROIs) traced on MRIs were transferred to the coregistered PET images. Cerebellar white matter was used as the reference region (Parsey *et al*, 2005) and the volume of distribution (V_2) did not differ among the remitters, nonremitters, and control group ($F = 0.887$; $df = 2, 62$; $p = 0.417$). Regional distribution volumes of [^{11}C]WAY-100635 were derived using an arterial input function as described previously (Parsey *et al*, 2005). Cerebellar V_2 from a one tissue (1T) compartment model was used as a constraint for the K_1/k_2 ratio in the two tissue (2T) kinetic modeling of the ROI. BP was calculated as $(V_T - V_2)/f_1$, where f_1 is the free fraction in plasma.

Statistics

Statistical analyses performed included Student's *t*-test, one way analysis of variance, and linear mixed models analysis with subject as the random effect. Model fitting was computed using both SPSS 11 for Mac OSX (www.spss.com) and R (www.R-project.org). When multiple regions were considered in a single analysis, region was included as a fixed effect, and the analysis was performed on the natural log of BP, in order to account for heterogeneity of variances across regions. Significance was defined as $p < 0.05$ and *p*-values are reported without multiple comparison adjustment. All tests were two-sided.

RESULTS

Baseline HAM-D scores were comparable in nonremitters and remitters (Table 1, $p = 0.783$). By definition, at the 1-year time-point, nonremitters had significantly higher scores on the HAM-D (23.2 ± 8.8) than remitters (4.3 ± 3.5, $p < 0.001$). Nonremitters, remitters and controls did not differ in the injected mass of [^{11}C]WAY-100635

Table 1 Demographic, Clinical, and Genotype Characteristics

	Controls	Nonremitters	Remitters	*p*-values
Total *N*	43[a]	13	9	
Male *N* (%)	19 (44)	2 (15)	2 (22)	0.110
Female *N* (%)	24 (56)	11 (85)	7 (78)	
No prior meds *N* (%)		5 (38)	3 (33)	0.584
Prior meds *N* (%)		8 (62)	6 (67)	
Age	38.2 ± 15.0	42.9 ± 14.9	37.9 ± 10.4	0.576
HRSD 24 baseline	0.698 ± 0.964	26.5 ± 7.4	25.6 ± 7.6	<0.001
HRSD 24 1 year		23.2 ± 8.8	4.3 ± 3.5	<0.001
Aggression score	13.7 ± 3.2	14.7 ± 3.8	15.8 ± 4.3	0.235
Adequate med trial at 1 year		8	5	1.000
On meds at 1 year		8	6	1.000
Met criteria for MDD at 1 year		8	3	0.387
Exposure to				
SSRI		9	7	1.000
Tricyclic		2	1	1.000
ECT		0	1	0.409
MOAI		1	0	1.000
Venlafaxine		2	1	1.000
Buproprion		4	3	1.000
Genotype distribution (%)				
CC	12 (28)	3 (23)	2 (22)	
CG	25 (60)	3 (23)	5 (56)	
GG	5 (12)	7 (54)	2 (22)	
χ^2		10.70	0.70	
p-Values		0.005	0.703	
Allele frequency (%)				
C	49 (58)	9 (35)	9 (50)	
G	35 (42)	17 (65)	9 (50)	
χ^2		3.58	0.149	
p-Values		0.058[b]	0.700	

[a]One control is not genotyped.
[b]Fisher's exact (one-tail) $p = 0.029$.

(controls = 6.9 ± 4.5 nmol; nonremitters = 6.1 ± 2.5 nmol; remitters = 5.0 ± 2.4 nmol) or injected dose of [^{11}C]WAY-100635 (controls = 8.4 ± 3.6 mCi, nonremitters = 10.4 ± 4.4 mCi; remitters = 8.3 ± 3.4 mCi). There is a difference in f_1 among the three groups ($F = 7.87$; $df = 2, 62$; $p = 0.0009$; controls = 8.1 ± 2.6; nonremitters = 5.7 ± 2.9; remitters = 8.5 ± 2.3, Figure 1). The non-remitter group had higher 5-HT$_{1A}$ BP ($((V_T - V_2)/f_1)$) compared with the remitter group across all brain regions ($F = 5.29$; $df = 1, 61$; $p = 0.025$; see Figure 2). There was also a significant interaction of responder status with region ($F = 3.87$; $df = 12, 744$; $p < 0.001$), and the difference was significant ($p < 0.05$, uncorrected for multiple comparisons) for each region except amygdala (AMY, $p = 0.054$) and raphe nucleus (RN, $p = 0.517$), although none of the region-specific comparisons would survive a Bonferroni correction.

The nonremitter and remitter groups did not differ in the adequacy of treatment during the year between the scan and the 1-year follow-up assessments as measured by the ATHF score (nonremitters = 2.6 ± 1.7; remitters = 2.9 ± 1.3, $p = 0.691$). They also did not differ in any demographic variables measured (Table 1). We have previously reported higher BP in AN medication-free MDD subjects compared to subjects who had previous exposure to antidepressants (Parsey *et al*, in press) and so this effect was included in the model. We found no interaction between prior medication status and remission status ($F = 0.158$; $df = 1, 62$; $p = 0.693$). Including age, sex, and lifetime aggression (Parsey *et al*, 2002) in the model did not affect the results; remitter status remained significant ($F = 4.33$; $df = 1, 57$; $p = 0.042$).

We report that depressed subjects and controls with at least one G allele of the C-1019G polymorphism have higher BP in the raphe (Parsey *et al*, in press). We found an association in genotype distribution ($\chi^2 = 10.7$, $df = 2$, $p = 0.005$) but not in allele frequency ($\chi^2 = 3.58$, $df = 1$, $p = 0.058$) between the control group and nonremitters (Table 1). Nonremitters have 3.5-fold greater incidence of GG genotype than remitters.

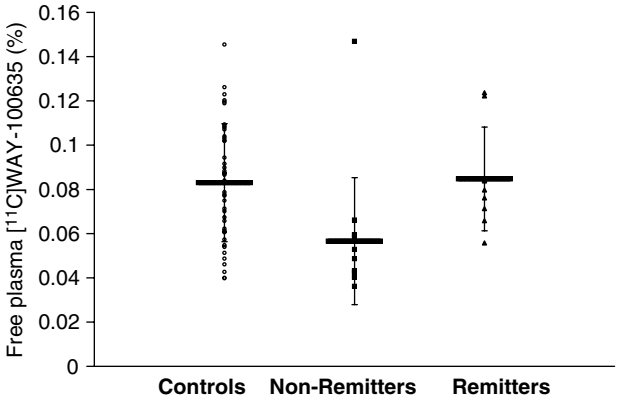

Figure 1 Percentage of free plasma [^{11}C]WAY-100635 (%) in plasma is different among the three groups ($p = 0.0009$). Solid horizontal bars are the means and the vertical bars are SD.

DISCUSSION

Nonremission of major depression after 1 year of community-based treatment is associated with higher pretreatment 5-HT$_{1A}$ BP and the higher expressing GG genotype. These data suggest the following 5-HT$_{1A}$ model for MDD: the GG polymorphism is associated with greater 5-HT$_{1A}$ gene expression in the RN and hence more 5-HT$_{1A}$ binding. As the 5-HT$_{1A}$ receptors are presynaptic, more 5-HT$_{1A}$ raphe autoreceptors would result in less serotonin neuron firing and decreased terminal field 5-HT release. This could be followed by a homeostatic upregulation of postsynaptic terminal field 5-HT$_{1A}$ receptors. The GG genotype is also associated with resistance to a variety of antidepressant treatments (Albert, 2004; Lemonde *et al*, 2004). Our data are consistent with this hypothesis; treatment resistant MDD have higher 5-HT$_{1A}$ receptors. Although we observe apparently higher mean autoreceptor 5-HT$_{1A}$ in GG

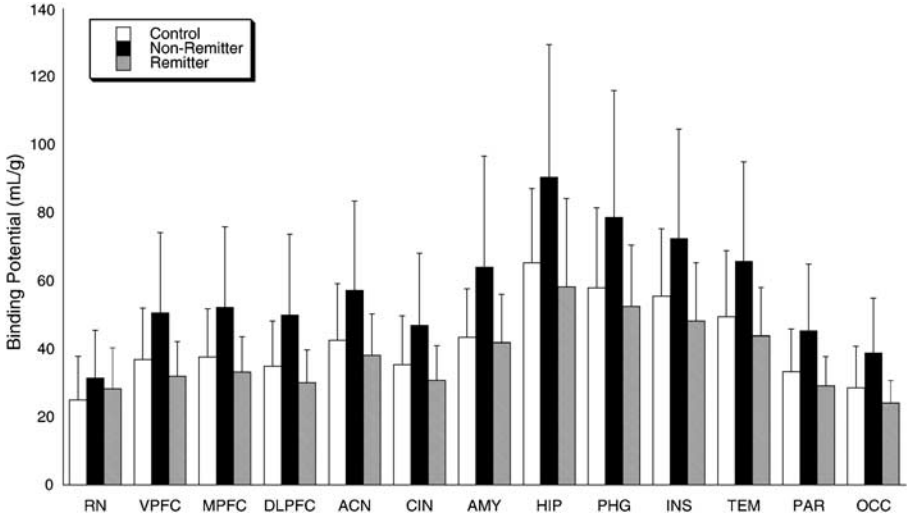

Figure 2 Nonremitters have increased BP across regions compared to remitters and controls (RN = raphe nuclei, VPFC = ventral prefrontal cortex, MPFC = medial PFC, DLPFC = dorsolateral PFC, ACN = anterior cingulate, CIN = cingulate body, AMY = amygdala, HIP = hippocampus, PHG = parahippocampal gyrus, INS = insula, TEM = temporal cortex, PAR = parietal cortex, OCC = occipital cortex).

nonremitter subjects in the raphe, the effect is not statistically significant perhaps due to power limitations due to sample size and a lower signal to noise ratio in this small ROI. If it can be confirmed that there are more 5-HT$_{1A}$ autoreceptors in nonremitters, then these subjects may be resistant to treatment because the genetic variant may interfere with SSRI-mediated desensitization or down-regulation of the presynaptic 5-HT$_{1A}$ autoreceptors (Paul Albert, personal communication and (Blier *et al*, 1987)). A striking observation is that the remitters have 5-HT$_{1A}$ binding comparable to the controls. Perhaps they respond to medication, particularly SSRIs because their serotonin system is less compromised biologically and genetically.

One nonremitter had an unusually large measurement for f_1 relative to the others (Figure 1). Repeating the analysis with this subject removed did not change the conclusions, as the effect of remitter status was still significant ($F = 7.79$; $df = 1, 60$; $p = 0.007$).

We have previously shown that MDD subjects who were never medicated had higher 5-HT$_{1A}$ BP than previously medicated and control subjects. This finding is unrelated to the current finding; there is no relationship between medication status and treatment response. The findings of increased 5-HT$_{1A}$ BP in never medicated MDD subjects is at odds with some of the previously published *in vivo* and *in vitro* data and have been discussed extensively elsewhere (Parsey *et al*, in press). For *in vivo studies*, differences in image acquisition, analysis, previous exposure to antidepressant medications, and patient populations may account for these discrepancies. For *in vitro* studies, in all cases, the controls are compared to suicide victims who have Axis I diagnoses, most commonly MDD. None of the published studies, to our knowledge, has compared controls to MDD subjects without suicide. None of these studies has examined the ability of 5-HT$_{1A}$ receptors to predict treatment response.

This study is not a prospective study with a controlled antidepressant treatment; rather it was an exploratory analysis of open, un-blinded, community-based treatment. Future studies should compare prediction of serotonin-selective and norepinephrine-selective antidepressants to see if outcome prediction is comparable for these different classes of medication. The current sample is relatively small and the results are preliminary.

Conclusions

This preliminary naturalistic study indicates that higher 5-HT$_{1A}$ binding is associated with a poorer response to antidepressant treatment and that MDD subjects who failed to respond to antidepressant treatment were more like to posses the GG genotype. Future prospective studies with a standardized treatment in a larger cohort are needed to determine the utility of 5-HT$_{1A}$ binding or genotype in treatment planning.

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