Brief Communication

A Functional Genetic Variation of the Serotonin (5-HT) Transporter Affects 5-HT$_{1A}$ Receptor Binding in Humans

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In humans, 5-HT$_{1A}$ receptors are implicated in anxiety and depressive disorders and their treatment. However, the physiological and genetic factors controlling 5-HT$_{1A}$ receptor expression are undetermined in health and disease. In this study, the influence of two genetic factors on 5-HT$_{1A}$ receptor expression in the living human brain was assessed using the 5-HT$_{1A}$-selective positron emission tomography (PET) ligand [^{11}C]WAY 100635. After the genotyping of 140 healthy volunteers to study population frequencies of known single nucleotide polymorphisms (SNPs) in the 5-HT$_{1A}$ receptor gene, the influence of the common SNP [(−1018) C>G] on 5-HT$_{1A}$ receptor expression was examined in a group of 35 healthy individuals scanned with [^{11}C]WAY 100635. In the PET group, we also studied the influence of a common variable number tandem repeat polymorphism [short (S) and long (L) alleles] of the 5-HT transporter (5-HTT) gene on 5-HT$_{1A}$ receptor density. Whereas, the 5-HT$_{1A}$ receptor genotype did not show any significant effects on [^{11}C]WAY 100635 binding, 5-HT$_{1A}$ receptor binding potential values were lower in all brain regions in subjects with 5-HTTLPR short (SS or SL) genotypes than those with long (LL) genotypes. Although the PET groups are necessarily a small sample size for a genetic association study, our results demonstrate for the first time that a functional polymorphism in the 5-HTT gene, but not the 5-HT$_{1A}$ receptor gene, affects 5-HT$_{1A}$ receptor availability in man. The results may offer a plausible physiological mechanism underlying the association between 5-HTTLPR genotype, behavioral traits, and mood states.

Key words: **serotonin; 5-HT$_{1A}$ receptor; serotonin transporter; genetics; polymorphisms; positron emission tomography**

Introduction

The neurotransmitter serotonin (5-HT) has been implicated in mood regulation and the pathophysiology and treatment of depression. The 5-HT$_{1A}$ receptor subtype appears to be critical for such functions because 5-HT$_{1A}$ receptors have high density in limbic and cortical regions involved in mood regulation, 5-HT$_{1A}$ agonists are anxiolytic, and antidepressant and recent positron emission tomography (PET) studies have reported reduced 5-HT$_{1A}$ receptor binding in patients with major depressive disorder (Drevets et al., 1999; Sargent et al., 2000; Bhagwagar et al., 2004), panic disorder (Neumeister et al., 2004), and associations with anxiety (Tauscher et al., 2001a) and aggression traits (Parsey et al., 2002). Furthermore, 5-HT$_{1A}$ autoreceptors, located on serotonergic raphe neurons, mediate negative feedback inhibition of these neurons and are desensitized after chronic antidepressant treatment with selective serotonin reuptake inhibitors (Blier et al., 1998). Finally, Lemonde et al. (2003) have suggested a transcriptional model in which a single nucleotide polymorphism of the 5-HT$_{1A}$ receptor gene derepresses 5-HT$_{1A}$ autoreceptor expression (thus increasing the 5-HT$_{1A}$ autoreceptor density in the raphe nucleus) to reduce serotonergic neurotransmission, predisposing to depression and suicide.

There are few known physiological regulators of 5-HT$_{1A}$ receptor expression *in vivo* short of extreme neuroendocrine manipulations (e.g., adrenalectomy). Genetic factors might be important determinants of 5-HT$_{1A}$ receptor function and thus influence mood state and response to psychotropic drug treatments. We therefore investigated the effects of polymorphisms of the 5-HT$_{1A}$ receptor and 5-HT transporter (5-HTT) genes on 5-HT$_{1A}$ receptor binding potential (BP) in humans using PET and [^{11}C]WAY 100635, a radioligand selective for 5-HT$_{1A}$ receptors. Specifically, we studied (1) whether a common promoter single nucleotide polymorphism (SNP) in the 5-HT$_{1A}$ receptor gene [(−1018) C>G] (Wu and Comings, 1999), which inhibits the repression of transcription (Lemonde et al., 2003), affects human 5-HT$_{1A}$ receptor BP and (2) whether a 44 bp insertion/deletion polymorphism located ~1 kb from the transcription initiation site of the 5-HTT gene, termed "5-HTTLPR" (Lesch et

Received Sept. 10, 2004; revised Jan. 28, 2005; accepted Jan. 29, 2005.

We thank Dr. Federico Turkheimer for his advice on statistical analysis and Renuka Adibhatla for her help with the WAY database. R.T.W. is Chief Scientific Officer for g-Nostics Ltd.

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DOI:10.1523/JNEUROSCI.3769-04.2005

 0270-6474/05/252586-05$15.00/0

al., 1996), would influence 5-HT_{1A} receptor BP. We chose to study the 5-HTTLPR because 5-HTT knock-out mice have reduced mRNA expression and density of 5-HT_{1A} receptors (Li et al., 2000).

Materials and Methods

Two separate groups of healthy volunteers were included in this study. The first cohort consisted of 140 healthy British Caucasian subjects (64 males, mean ± SD age of 51.5 ± 8.8 years; 76 females, mean ± SD age of 52.4 ± 8.8 years; whole group, mean ± SD age of 52.0 ± 8.8 years) who were randomly selected from the OXCHECK study (Imperial Cancer Research Fund, 1995), this cohort was genotyped to study the population frequencies of known SNPs in the 5-HT_{1A} receptor gene. All subjects in the OXCHECK study underwent a general health check with their general practitioner, and none of them had any reported mood or anxiety disorders. The second group of 35 healthy volunteers (27 males, mean ± SD age of 43.6 ± 13.1 years; eight females, mean ± SD age of 52.6 ± 10.3 years; whole group, mean ± SD age of 46 ± 13 years), who had undergone PET scans using [^{11}C]WAY 100635, a specific radioligand for 5-HT_{1A} receptors, were genotyped to study the influence of two genetic factors on 5-HT_{1A} receptor BP. All except six subjects were from our reported database of [^{11}C]WAY 100635 scans (Rabiner et al., 2002). All participants in the PET group had undergone psychiatric screening (including substance/alcohol use history) and physical examination by a qualified clinician. Furthermore, the general practitioners of all the consenting volunteers were contacted to confirm their health status. None of the participants met DSM IIIR (*Diagnostic and Statistical Manual of Mental Disorders*, third edition, revised) criteria for current or past depressive or anxiety disorders, and all were physically healthy. All subjects gave written informed consent, and the local research ethics committee approved the study.

A literature search identified nine SNPs in the 5-HT_{1A} receptor gene (Nakhai et al., 1995; Lam et al., 1996; Kawanishi et al., 1998; Wu and Comings, 1999). For the panel of healthy Caucasians from the OXCHECK cohort, assays were developed for each SNP, and genotyping was conducted on DNA to identify informative haplotypes in the 5-HT_{1A} receptor gene (chromosome 5q11.2-q13) (supplemental Table 1, available at www.jneurosci.org as supplemental material). Genomic DNA was extracted from buffy coat lymphocytes using a standard sodium chloride–chloroform technique and stored in sterile distilled water at −20°C. The genotyping assay was performed as described by Bunce et al. (1995), using sequence-specific primers. PCRs were performed for both the common and variant alleles, and each reaction contained control primers to detect a conserved sequence in the *adenomatosis polyposis coli* gene, thereby eliminating the possibility of false-negative results.

In the latter part of the study, blood samples from the PET group of 35 subjects were genotyped for the 5-HT_{1A} receptor gene (5q11.2-q13) (Wu and Comings, 1999) SNP at the site [(−1018) C>G] (which was also found to be the only common SNP in the OXCHECK cohort of healthy volunteers) using the same PCR-based methods described previously. In addition, all subjects from the PET cohort were genotyped for 5-HTTLPR (17q11.1-q12) (Lesch et al., 1996) variable number tandem repeat polymorphism [short (S) and long (L)] using primers and conditions described previously (Lerman et al., 2000). The 5-HTTLPR assay results in either an inserted (long) variant of 528 bp or a deleted (short) variant of 484 bp (Lesch et al., 1996). In humans, the S allele of the 5-HTTLPR has been associated with decreased transcriptional activity and disrupted 5-HTT function (Lesch et al., 1996). Subjects were dichotomized as 5-HTTLPR (SS or SL vs LL) and 5-HT_{1A} (CC vs CG or GG), consistent with previous studies demonstrating autosomal dominance for the 5-HTTLPR S allele (Lesch et al., 1996) and 5-HT_{1A} G allele (Lemonde et al., 2003).

PET data acquisition and image analysis procedures have been described in detail previously (Rabiner et al., 2002). In brief, PET scans were performed on two scanners, an ECAT 953 ($n = 29$) and on an ECAT 966 ($n = 6$) scanner (CTI Positron Systems, Knoxville, TN). [^{11}C]WAY 100635 was injected intravenously as a bolus over 30 s, and the emission data were collected over 90 min and quantified via a simplified reference tissue model with cerebellum as the reference region. Binding potentials ($BP = f_2 B_{Avail}/K_D$, where f_2 is free fraction of the radioligand in the tissue, B_{Avail} is concentration of available binding sites, and K_D is equilibrium dissociation rate constant of the radioligand) were calculated for midbrain and corticolimbic regions of interest.

To analyze the effect of the (−1018) C>G SNP or 5-HTTLPR polymorphisms on 5-HT_{1A} receptor binding, multivariate repeated-measures ANOVA was performed. For each ANOVA, there were 21 brain regions as within-subject factors, and genotype [(−1018) C>G SNP or 5-HTTLPR], PET scanner, and gender were between-subject factors.

Table 1. Group characteristics and genotype frequencies for 5-HT_{1A} SNPs in population of healthy Caucasian volunteers

Locus	Genotype	Frequency ($n = 140$)	Percentage	Hardy–Weinberg (p value)
(−1018) C/G	CC	36	25.7	0.484
	CG	74	52.9	
	GG	30	21.4	
+82 A/G	AA	137	97.9	0.898
	AG	3	2.1	
	GG	0	0	
+549 C/T	CC	138	98.6	0.932
	CT	2	1.4	
	TT	0	0	
+656 G/T	GG	135	96.4	0.830
	GT	5	3.6	
	TT	0	0	

Genotype frequencies and percentages for 140 healthy Caucasian controls from the greater Oxfordshire, United Kingdom, region are listed. Genetic variation within this population was observed in only four of nine SNPs, for which Hardy-Weinberg equation values are indicated. Characteristics of the subjects are as follows: age, median of 51.7 years, range of 36.4–68 years; mean ± SD of 52.0 ± 8.8.

Results

Results from the genotyping of the healthy OXCHECK Caucasian panel are presented in Table 1. Of the nine loci in the 5-HT_{1A} receptor gene identified from public databases, only four were found to be polymorphic in our population. In line with previous studies, the SNP at the site (−1018) C>G was sufficiently common to allow group comparisons in the PET group.

Genotype frequencies of the 5-HT_{1A} receptor [(−1018) C>G] and 5-HTTLPR gene polymorphisms in the PET group of subjects conformed to the Hardy-Weinberg equilibrium (5-HT_{1A}, $\chi^2 = 0.10, p = 0.77$; 5-HTTLPR, $\chi^2 < 0.01, p = 0.88$). The 5-HT_{1A} receptor SNP at the site (−1018) C>G showed no significant effect on [^{11}C]WAY 100635 BP values (Fig. 1*a*,*c*; Table 2) in both postsynaptic (cortical and limbic) and presynaptic autoreceptor (midbrain raphe) (Fig. 1*c*) regions. In contrast, BP values in those with the 5-HTTLPR SS or SL genotype were significantly lower than in those with LL genotype allele (Fig. 1*b*; Table 2), and this was independent of the scanner and gender. BP values for the SL group were in between those of the homozygote groups, with the values being closer to the SS group. BP was higher in all brain regions in those with the LL genotype, with the most marked differences in the insula, precentral gyrus, inferior frontal gyrus, and anterior cingulate (Fig. 1*d*).

Discussion

The association of the S allele of the 5-HTTLPR gene polymorphism with reduced 5-HT_{1A} receptor BP is consistent with, and predicted by, studies in 5-HTT knock-out mice (Li et al., 2000) and thus shows the potential utility of mouse–human experimental parallels for the understanding of genetic effects on human brain function. Furthermore, this is the first human study to demonstrate effects of a 5-HTTLPR gene polymorphism on a functionally related but distinct receptor (5-HT_{1A} receptor). Mechanistically, the lower transcriptional efficiency associated

with the S allele of the 5-HTTLPR may lead to decreased 5-HTT function, which in turn may lead to a lifelong increase in 5-HT tone, which may in turn desensitize and downregulate 5-HT$_{1A}$ receptors.

In contrast, the lack of an effect of the 5-HT$_{1A}$ receptor gene (−1018) C>G SNP argues against the recent intriguing hypothesis that depressed patients with this polymorphism would show increased 5-HT$_{1A}$ autoreceptor expression at the raphe nucleus, thus mediating increased inhibition of serotonergic neurons (Lemonde et al., 2003). However, it is possible that partial volume effects may have reduced the sensitivity of detection of group differences in BP values in the measurement of a small structure such as raphe nucleus.

In the 5-HTT knock-out mice, the reduction in density of 5-HT$_{1A}$ receptors was region specific and more extensive in females (dorsal raphe only in male and hypothalamus and amygdala in addition in female) (Li et al., 2000). However, in our study involving healthy human volunteers, there was no significant gender effect, although the number of females in our sample was small. Furthermore, the region-specific effects appeared more widespread than reported in knock-out mice, particularly in cortical areas, although 5-HT$_{1A}$ receptor density measurements were reported only for a few cortical areas by Li et al. (2000) in knock-out mice. We also studied the confounding effects of age because two studies (Meltzer et al., 2001; Tauscher et al., 2001b) have shown an inverse relationship between age and [^{11}C]WAY 100635 binding (the former showed this effect only in men); however, two other studies (Parsey et al., 2002; Rabiner et al., 2002) have found no such relationship. In this study, when age was included as a covariate in the ANOVA model, there was no significant age effect ($F = 2.2$; df = 1,32; $p = 0.147$), and the allelic effect of the 5-HTTLPR on [^{11}C]WAY 100635 binding remained significant ($F = 5.7$; df = 1,32; $p = 0.023$).

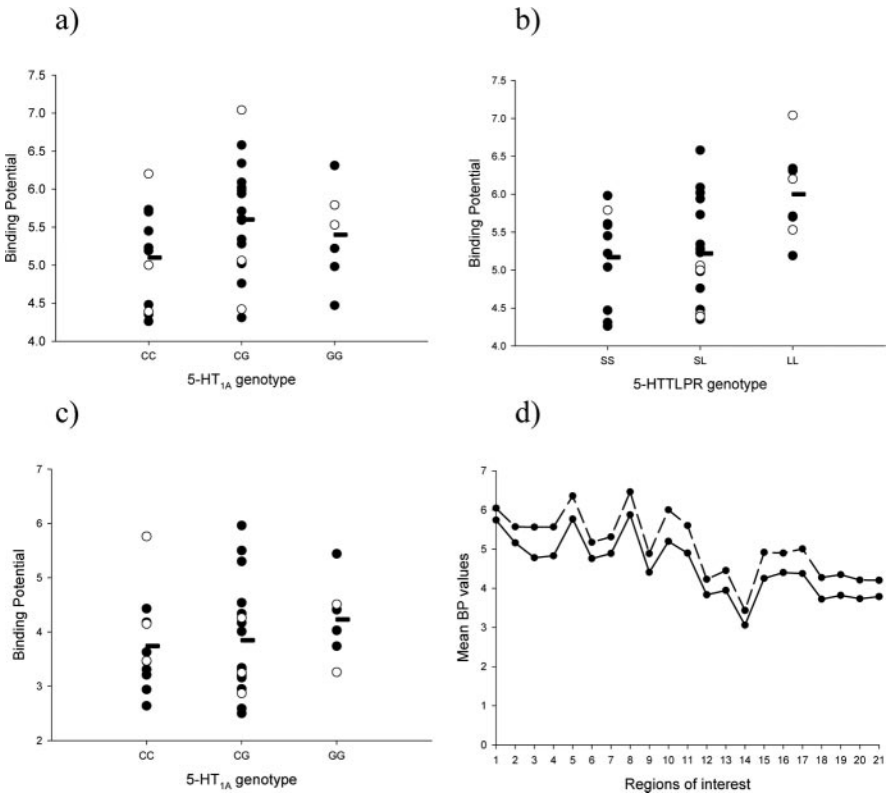

Figure 1. Genotypic and allelic comparison of [^{11}C]WAY 100635 binding potentials. ***a***, Scatter plot of BP values at insula by 5-HT$_{1A}$ receptor genotype. ***b***, Scatter plot of BP values at insula by 5-HTTLPR genotype. ***c***, Scatter plot of BP values at raphe nucleus by 5-HT$_{1A}$ receptor genotype. ***d***, Line graph of 5-HT$_{1A}$ receptor binding potential by 5-HTTLPR alleles (S vs L). ***a–c***, Black circles, Males; white circles, females; dashes, the mean. ***d***, Black circles with solid line, SS plus SL; black circles with hatched line, LL. The numbers in ***d*** correspond to the following regions: 1, hippocampus; 2, amygdala; 3, anterior medial temporal lobe*; 4, anterior lateral temporal lobe*; 5, parahippocampus*; 6, superior temporal gyrus; 7, medial inferior temporal gyrus; 8, fusiform gyrus; 9, posterior temporal gyrus*; 10, insula*; 11, anterior cingulate*; 12, posterior cingulate; 13, parietal lobe*; 14, occipital lobe; 15, orbitofrontal gyrus*; 16, gyrus frontomedialis*; 17, gyrus precentralis*; 18, gyrus frontoinferior*; 19, gyrus frontomedius*; 20, gyrus frontosuperior*; 21, raphe. *$p < 0.05$ indicates significant group difference after *post hoc t* test.

Many but not all studies have suggested an association between the S allele and abnormal mood states/emotional behaviors (Lesch et al., 1996; Mazzanti et al., 1998; Munafo et al., 2003), depressive illness (Willeit et al., 2003), severity of depressive

Table 2. [^{11}C]WAY 100635 BP values in the PET group and 5-HTTLPR and 5-HT$_{1A}$ receptor gene polymorphisms

	Region	SS ($n = 10$)	SL ($n = 17$)	LL ($n = 8$)	SS plus SL ($n = 27$)	LL ($n = 8$)
5-HTTLPR	Raphe	3.7 ± 1	3.8 ± 0.9	4.2 ± 0.8	3.8 ± 0.9	4.2 ± 0.8
	Postsynaptic[a]	4.1 ± 0.5	4.3 ± 0.5	4.7 ± 0.6	4.2 ± 0.5	4.7 ± 0.6
		GG ($n = 6$)	CG ($n = 18$)	CC ($n = 11$)	GG plus CG ($n = 24$)	CC ($n = 11$)
5-HT$_{1A}$ [(−1018) C>G]	Raphe	4.2 ± 0.7	3.8 ± 1	3.7 ± 0.9	3.9 ± 0.9	3.7 ± 0.9
	Postsynaptic[a]	4.4 ± 0.5	4.4 ± 0.6	4.1 ± 0.5	4.4 ± 0.5	4.1 ± 0.5

Values shown are mean ± SD.

[a]Mean ± SD BP values of 20 corticolimbic regions of interest.

5HTTLPR*: group allelic effect, $F = 4.8$, df = 1, 27, $p = 0.037$; scanner effect, $F = 2.3$, df = 1, 27, $p = 0.1$; gender effect, $F = 1.4$, df = 1, 27, $p = 0.3$; interaction effects, allele × scanner, $F = 0.3$, df = 1, 27, $p = 0.6$; allele × gender, $F = 2.5$, df = 1, 27, $p = 0.1$; scanner × gender, $F = 0.6$, df = 1, 27, $p = 0.5$; allele × scanner × gender, $F = 0.4$, df = 1, 27, $p = 0.5$.

5-HT$_{1A}$ (−1018c>G)**: group allelic effect, $F = 0.001$, df = 1, 28, $p = 0.973$; scanner effect, $F = 0.16$, df = 1, 28, $p = 0.9$; gender effect, $F = 2.1$, df = 1, 28, $p = 0.2$; interaction effects, allele × scanner, $F = 1.1$, df = 1, 28, $p = 0.3$; allele × gender, $F = 0.6$, df = 1, 28, $p = 0.4$; scanner × gender, $F = 1.7$, df = 1, 28, $p = 0.2$.

*Repeated-measures ANOVA comparing the SS plus SL versus LL groups.

** Repeated-measures ANOVA comparing the CC versus CG plus GG groups.

symptoms in Parkinson's disease (Mossner et al., 2001), suicidality (Anguelova et al., 2003), and neuroticism (Sen et al., 2004). Likewise, reduced 5-HTT availability (as found in those with S allele) has been demonstrated in living depressed patients in some but not all studies (Stockmeier, 2003). Our results suggest that the putative associations of the S allele with emotional behaviors and mood disorders may be mediated in part via reductions of 5-HT$_{1A}$ receptor density.

The possible limitations of this study include its retrospective design, small subject numbers, and the use of conventional *p* values in a genetic association study. The number of subjects that can be scanned using PET, as opposed to those that can be genotyped, is limited because of radiation exposure and cost constraints. A sample size of 35 subjects is a small number for a genetic study, but it is a large sample for a PET study and is consistent numerically with other recent neuroimaging studies showing plausible associations between polymorphisms and other imaging parameters such as functional magnetic resonance imaging responses to emotional face recognition (Hariri et al., 2002). Indeed, it has been suggested that emotional and affective neural systems, which can be imaged, may be more directly related to 5-HT functional polymorphisms than complex behaviors or psychiatric syndromes (Hariri and Weinberger, 2003). Although the validity of *post hoc* power calculations are debatable (Goodman and Berlin, 1994; Hoenig and Heisey, 2001), our power calculations showed that, for the 5-HT$_{1A}$ receptor gene (−1018) C>G SNP, we had a power of 89% to detect a 15% difference of BP between groups, with $\alpha = 0.05$. Thus, despite adequate power and a "conventional *p* value," we did not find an association between the 5-HT$_{1A}$ receptor gene (−1018) C>G SNP and 5-HT$_{1A}$ receptor binding. In contrast, for the 5-HTTLPR gene, we only had a power of 59% to detect the observed 1 SD [0.5 for postsynaptic regions (Table 2)] difference in BP between groups, with $\alpha = 0.05$. Thus, despite a low power, we found a significant association between 5-HTTLPR and 5-HT$_{1A}$ receptor binding. It is known that nonreplication of candidate gene studies attributable to the use of conventional significance levels is a potential problem in genetic association studies. For this reason, we only tested two genetic markers for association with 5-HT$_{1A}$ receptor binding potentials. These loci were chosen on the basis of rigorous biological hypotheses derived from existing high-quality studies (Li et al., 2000; Lemonde et al., 2003). Thus, the prior probability of association (Wacholder et al., 2004) is likely to be higher for these loci than for those for which the prior probability of association is low (i.e., in the case of a genome-wide scan or a randomly selected SNP). As pointed out by Wacholder et al. (2004), the likelihood of a false-positive report is a function of the prior probability of the hypothesized association being meaningful, which in this case is based on published data of the functional effects of the specific genetic variants. As advocated by Wacholder et al. (2004), we integrated animal functional data on the genetic variant into our hypothesis rather than randomly selecting genetic markers.

In summary, this *in vivo* human imaging study shows that genomic effects can extend beyond the receptor targeted by the gene to functionally related systems and more specifically provides a plausible mechanistic explanation as to how 5-HTTLPR allelic frequencies may influence the expression of dysfunctional moods and personality traits.

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