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Reduced ventral striatal/ventral pallidal serotonin$_{1B}$ receptor binding potential in major depressive disorder

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Abstract

Rationale—Although serotonin (5-HT) dysregulation is implicated in the pathophysiology of major depressive disorder (MDD), the role of specific receptor subtypes remains to be elucidated. Emerging preclinical research suggests an important role for the 5-HT$_{1B}$ receptor in behavioral regulation and depressive phenotypes. In particular, 5-HT$_{1B}$ heteroreceptors located within the striatum have been shown to play an essential role in antidepressant action.

Objectives—The objective of this study was to determine 5-HT$_{1B}$ receptor binding potential (BP_{ND}) in the region of the ventral striatum/ventral pallidum (VS/VP) in individuals with MDD and healthy control participants.

Methods—Ten participants with MDD (30.8±9.5 years, five men/five women) in a current major depressive episode (MDE) and ten healthy control participants (30.7±10.5 years, five men/five

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women) underwent positron emission tomography (PET) scanning with the selective 5-HT_{1B} receptor radioligand [^{11}C]P943.

Results—Within the VS/VP region of interest, [^{11}C]P943 BP_{ND} was significantly reduced in the MDD group compared with the healthy control group (1.37±0.13 and 1.68±0.16, respectively; 18.7% between-group difference; $p<0.001$).

Conclusions—Consistent with preclinical and postmortem data, our findings suggest abnormally reduced function of VS/VP 5-HT_{1B} receptors in humans with MDD. Abnormal 5-HT_{1B} heteroreceptor function may contribute to dysfunctional reward signaling within the striatum, including the nucleus accumbens, via interaction with dopamine, γ-amino-butyric acid, or glutamate systems. Our findings suggest reduced 5-HT_{1B} receptor signaling in the VS/VP in MDD and contribute to the therapeutic rationale for testing 5-HT_{1B} agonists as a novel class of antidepressants.

Keywords

Major depressive disorder; Human subjects; Brain imaging; Serotonin; Serotonin$_{1B}$ receptor; Positron emission tomography; Ventral striatum

Introduction

Abundant research implicates altered serotonin (5-HT) function in major depressive disorder (MDD) (Heninger et al. 1984; Jans et al. 2007; Belmaker and Agam 2008; aan het Rot et al. 2009). Replicated findings in support of deficient 5-HT function include reduced 5-HT metabolites in the plasma and cerebrospinal fluid (CSF) of depressed patients, depressiogenic effects of acute tryptophan depletion (ATD) in vulnerable individuals, and the efficacy of 5-HT reuptake inhibitors in the treatment of depressive symptoms (Neumeister et al. 2004, 2006; Jans et al. 2007). However, the precise role of 5-HT or its numerous receptor subtypes in the pathophysiology of depression remains to be characterized.

Positron emission tomography (PET) neuroreceptor studies of the 5-HT_{1A} receptor in humans have demonstrated reduced receptor binding potential (BP_{ND}) (Innis et al. 2007) within a cortico-limbic-striatal circuit during both acute depressive episode and remission (Drevets et al. 1999; Bhagwagar et al. 2004; Drevets et al. 2007; Savitz et al. 2009). Although changes in the 1A receptor appear to be associated with depression, it is clear that alterations in this receptor would account for only a portion of the putative dysregulated 5-HT neurotransmission in the pathophysiology of the disorder.

Growing preclinical evidence suggests an important role of the 5-HT_{1B} receptor in depression (Sari 2004; Svenningsson et al. 2006; Chenu et al. 2008; Ruf and Bhagwagar 2009). The 5-HT_{1B} receptor is an inhibitory G protein-coupled metabotropic receptor found primarily as presynaptic terminal auto- and heteroreceptors on 5-HT and non-5-HT neurons, respectively (Pauwels 1997; Hoyer et al. 2002; Hannon and Hoyer 2008). In the mammalian central nervous system (CNS), 5-HT_{1B} receptors are widely distributed, with particularly high densities occurring in the striatum and pallidum (Pauwels 1997; Hoyer et al. 2002). Given the emerging role of the striatum and globus pallidus, particularly ventral regions encompassing the nucleus accumbens (NAc), in the functional neuroanatomy of depression (Nestler and Carlezon 2006; Krishnan and Nestler 2008; Carlezon and Thomas 2009), the high levels of 5-HT_{1B} receptors in these regions may further suggest an important role for this receptor subtype in the pathophysiology of the disorder.

The aim of the current study was to characterize 5-HT_{1B} receptor function in the region of the ventral striatum/ventral pallidum (VS/VP) in MDD using the selective 5-HT_{1B} receptor radioligand [^{11}C]P943 (Nabulsi et al. 2010). Recent evidence suggests that 5-HT_{1B} receptor expression is decreased in an animal model of depression and that p11, an important intracellular protein involved in 5-HT_{1B} signaling, is decreased in postmortem brains of depressed patients (Svenningsson et al. 2006). Therefore, we hypothesized that patients with MDD would exhibit reduced [^{11}C]P943 BP_{ND} in VS/VP, reflecting low levels of 5-HT_{1B} expression in this region.

Methods and materials

Subjects

Ten participants with MDD in a current major depressive episode (MDE) and ten healthy control participants were recruited through public advertisement. Participants were screened and diagnosed using Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria and the Structured Clinical Interview for DSM-IV (SCID) administered by an experienced clinician (First et al. 1995; APA 2000). Depression and anxiety severity were assessed using the Montgomery–Asberg Depression Rating Scale (MADRS) and the Hamilton Rating Scale for Anxiety (HAM-A), respectively (Hamilton 1959; Montgomery and Asberg 1979). Smoking status was assessed with the Fagerstrom Test for Nicotine Dependence (FTND) (Heatherton et al. 1991); family history of depression was assessed using a modified version of the Family Interview for Genetic Studies (FIGS) (Maxwell 1992). All participants were evaluated by physical examination, electrocardiogram, standard laboratory tests, urine analysis, and toxicology. Participants with significant medical or neurological conditions or with history of head injury with loss of consciousness were excluded from the study. All scans with female participants were conducted, while participants were in the follicular phase of their menstrual cycle in order to control for the effects of hormonal variation on PET measures. The protocol was approved by the Yale University School of Medicine Human Investigation Committee, the Human Subjects Subcommittee of the Veterans Affairs Connecticut Healthcare System, the Magnetic Resonance Research Center, and the Yale New Haven Hospital Radiation Safety Committee. Written informed consent was obtained from all participants after full explanation of study procedures.

Scanning and imaging procedures

Subject preparation for the PET scan consisted of indwelling venous catheter placement. A transmission scan using a ^{137}Cs point source was obtained before the emission scan. The PET scans were acquired for 120 min at rest using a single intravenous injection of high-specific activity [^{11}C]P943, a selective 5-HT_{1B} receptor antagonist radiotracer (Nabulsi et al. 2010), on an HRRT PET scanner (207 slices, resolution less than 3 mm full-width at half-maximum in 3D acquisition mode). Dynamic scan data were reconstructed with corrections (attenuation, normalization, scatter, randoms, and deadtime). Motion correction of PET data was performed by coregistering each reconstructed frame to an early summed image (0–10 min postinjection) using a six-parameter mutual information algorithm and FMRIB's Linear Image Registration Tool (FLIRT, FSL 3.2, Analysis Group, FMRIB, Oxford, UK).

Magnetic resonance (MR) images were obtained for each subject on a Siemens 3T Trio system to exclude individuals with anatomical abnormalities and for co-registration. A second summed image (0–10 min postinjection) was created from the motion-corrected PET data and registered to the subject's MR image, which in turn, was registered (12-parameter affine transformation) to an MR template (MNI space). The VS/VP region of interest (ROI) was taken from the template for SPM2 (Anatomical Automatic Labeling) and applied to the

PET data to produce time–activity curves for the ROI, in reference to the cerebellum (Tzourio-Mazoyer et al. 2002). Pixel-by-pixel analysis was performed using the multilinear reference tissue model, MRTM2 (Ichise et al. 2003), to produce images of BP_{ND} (Innis et al. 2007). The interpretation of BP_{ND} is f_{ND}* Bavail/Kd where f_{ND} is the tracer-free fraction in a region without specific binding, Bavail is the unoccupied receptor concentration, and Kd is the dissociation equilibrium constant of the tracer. The cerebellum was used as the reference region since it is essentially devoid of 5-HT_{1B} receptors (Varnas et al. 2005). Assuming that there is no change in affinity or non-specific binding between subject groups, changes in BP_{ND} were interpreted as changes in receptor concentration. BP_{ND} values from MRTM2 have provided highly comparable results to those obtained with arterial input functions (Gallezot et al. 2010).

Statistical analysis

Independent sample *t* tests were used to compare continuous clinical and demographic variables and [^{11}C]P943 BP_{ND} values between MDD and control groups. Data were normally distributed as determined by visual inspection and the Kolmogorov–Smirnov *D* test. Chi-square was used in the case of dichotomous variables. Tests of association between continuous variables were performed using Pearson's product-moment correlations. All tests were performed two-tailed, with results considered significant at $p<0.05$. Means and standard deviations are reported unless otherwise noted. All statistical analyses were conducted using SPSS version 16.0 (SPSS Inc, Chicago, IL, USA).

Results

Demographics and clinical characteristics

Participants were matched for age and gender (HC, 30.7±10.5 years, 5M/5F; MDD, 30.8±9.5 years, 5M/5F; see Table 1). Participants with MDD were outpatients with moderate severity depression (MARDS score, 23.9±5.0) and were free of comorbid axis I disorders. All MDD participants had recurrent episodes, onset of illness before 21 years of age, and a family history positive for depression (at least one first degree blood relative afflicted). The mean duration of the current major depressive episode was 9.4±5.3 months (range, 4 to 20 months). Participants with MDD were antidepressant treatment naïve, except one participant who had a previous trial of an SSRI; all participants were free of any psychotropic medication for at least 4 weeks prior to the time of the PET scan.

Neuroreceptor imaging

Within our bilateral combined VS/VP ROI, [^{11}C]P943 BP_{ND} was significantly reduced in the MDD group compared to the healthy control group (1.37±0.13 and 1.68±0.16, respectively; 18.7% between-group difference; $p<0.001$) (Fig. 1). Both right and left individual ROIs were also significantly different between groups (left hemisphere, 1.35±0.13 and 1.61±0.15, respectively; 16.1% between-group difference; $p=0.001$; right hemisphere, 1.38±0.24 and 1.75±0.26, respectively; 21.1% between-group difference; $p=0.004$).

[^{11}C]P943 BP_{ND} did not correlate with any clinical or demographic measures or the PET injection parameters.

Discussion

In this study, we found significantly reduced [^{11}C]P943 BP_{ND} in VS/VP in MDD compared with healthy control participants. To our knowledge, this report is the first direct evidence that abnormal brain 5-HT_{1B} receptor expression is associated with depression in humans.

Our findings are consistent with the recent report of low postmortem levels of the 5-HT_{1B} related protein p11 in brains of depressed patients (Svenningsson et al. 2006). P11 appears to play a critical role in 5-HT_{1B} receptor intracellular trafficking and cell surface expression specifically, and low p11 mRNA transcription directly corresponds to low 5-HT_{1B} receptor function in animals (Svenningsson et al. 2006). Notably, antidepressant medications or electroconvulsive administration enhanced p11 mRNA in mice, and over-expression of p11 conferred antidepressant properties in a mouse model, whereas p11 knockout resulted in a depressive phenotype (Svenningsson et al. 2006). These preclinical findings are in agreement with previous studies demonstrating decreased depressive and anxious behavior in animal models as a result of 5-HT_{1B} agonists (Tatarczynska et al. 2004; Chenu et al. 2008) (however, conflicting results are reported, see (Ruf and Bhagwagar 2009) for review). Previous studies in humans have suggested 5-HT_{1B} receptor hypofunction in depression based upon blunted growth hormone (GH) responses to administration of the 5-$HT_{1D/1B}$ agonists sumatriptan or zolmitriptan (Cleare et al. 1998; Whale et al. 2001).

Anatomically, we chose to focus on the VS/VP due to the high levels of 5-HT_{1B} receptor expression in this region (Sari 2004) and the prominent role of this region in neurocircuitry models of depression (Nestler and Carlezon 2006; Krishnan and Nestler 2008; Carlezon and Thomas 2009). The NAc (anatomically overlapping with the ventral striatum), a key substrate for reward and motivated behavior, receives 5-HTergic innervation from the dorsal raphe and DAergic innervation from the ventral tegmental area (VTA), as well as glutamateric input from prefrontal cortex (PFC) and hippocampus (Nestler and Carlezon 2006). Recently, attenuated activation in this region has been observed in response to positive stimuli in patients with MDD using functional magnetic resonance imaging (Epstein et al. 2006; Pizzagalli et al. 2009). Serotonin$_{1B}$ terminal autoreceptors in this region would be expected to reduce activity of 5-HT neurons, while terminal heteroreceptors would be expected to reduce activity in non-5-HT neurons, for example DAergic, glutamatergic, or GABAergic (Hoyer et al. 2002). However, 5-HT_{1B} agonists were shown to facilitate, rather than inhibit, DA release in the NAc of rats (Yan and Yan 2001). Further, the antidepressant effects of the 5-HT_{1B} agonist anpirtoline in the forced swim test were found to specifically depend on the 5-HT_{1B} heteroreceptor, rather than the autoreceptor, suggesting that 5-HT_{1B} modulation of DAergic function may mediate the antidepressant effect (Chenu et al. 2008). Our finding of low VS/VP 5-HT_{1B} receptor density is consistent with hypothesized dysfunction of DA transmission, in addition to 5-HT transmission, in MDD (Meyer et al. 2006; Nestler and Carlezon 2006; Hasler et al. 2008).

The finding of low [^{11}C]P943 BP_{ND} in MDD extends the preclinical findings of low p11 and 5-HT_{1B} receptor function in animal models (Svenningsson et al. 2006) and adds to the therapeutic rationale for testing 5-HT_{1B} agonists as a novel class of antidepressants. Although preclinical data is mixed regarding the antidepressant effects of 5-HT_{1B} agonists (Ruf and Bhagwagar 2009), receptor localization needs to be considered to determine the impact this receptor subtype has on depression and antidepressant mechanisms. It is quite likely that 5-HT_{1B} receptors are involved in distinct if not opposing processes in depression, potentially accounting for conflicting preclinical results. For example, Chenu et al. demonstrated that 5-HT_{1B} heteroreceptors on non-serotoninergic neurons were specifically required for the antidepressant effects of an SRI in the forced swim test (Chenu et al. 2008). Further, the authors reported a specific antidepressant effect of a 5-HT_{1B} agonist when infused into the caudate and putamen, however, not when infused into the hippocampus, substantia nigra, or frontal cortex (Chenu et al. 2008). Our finding of regional VS/VP reduction of 5-HT_{1B} receptors may support the hypothesis that 5-HT_{1B} agonists would possess antidepressant properties specifically via their interaction with 5-HT_{1B} heteroreceptors located on DAergic neurons in limbic regions of the basal ganglia.

This study has several limitations. The relatively small sample size of the groups limits the inference that can be drawn regarding depression pathophysiology in the broader population. Our MDD sample was very well characterized and relatively homogenous, early-onset, recurrent with positive family history of depression, and treatment naïve with one exception. This homogeneity may have enhanced our ability to detect a biological signal. However, there is a need to expand the sample to include a broader range of depressive illness phenotypes. Further, we are unable to determine if our finding represents a trait or state feature for MDD. Likewise, we are unable to establish if low5-HT_{1B} receptor binding represents a preexisting vulnerability factor, or rather develops as a consequence of the illness. Lastly, tobacco use was comorbid in our MDD sample (three MDD participants were current smokers vs none in the HC group) and may potentially impact 5-HT_{1B} signaling by virtue of its influence on striatal DA function (Brody et al. 2009). Our sample size did not allow us to address the influence of smoking status on our findings, and future studies will be needed to clarify the potential role of smokingon5-HT_{1B} function sufficiently.

Future neuroreceptor studies will be needed to address several important research questions, including the specificity of 5-HT_{1B} receptor dysfunction to MDD. Serotonin dysfunction appears to be an important biological factor in several psychiatric disorders, including anxiety and substance disorders, in addition to MDD (Jans et al. 2007). Our group recently published an initial finding of elevated [^{11}C]P943 BP_{ND} in VS/VP in alcohol dependence (Hu et al. 2010). Although the pathological implications of these changes in MDD and alcohol dependence remain unclear, the opposite directionality of the signal in the two disorders may suggest the potential for diagnostic specificity.

In conclusion, we have demonstrated a significant reduction in VS/VP [^{11}C]P943 BP_{ND} in MDD, suggestive of reduced 5-HT_{1B} receptor expression in the disorder. Despite its complex pharmacology, the 5-HT_{1B} receptor may represent an important new target in depression research and therapeutics.

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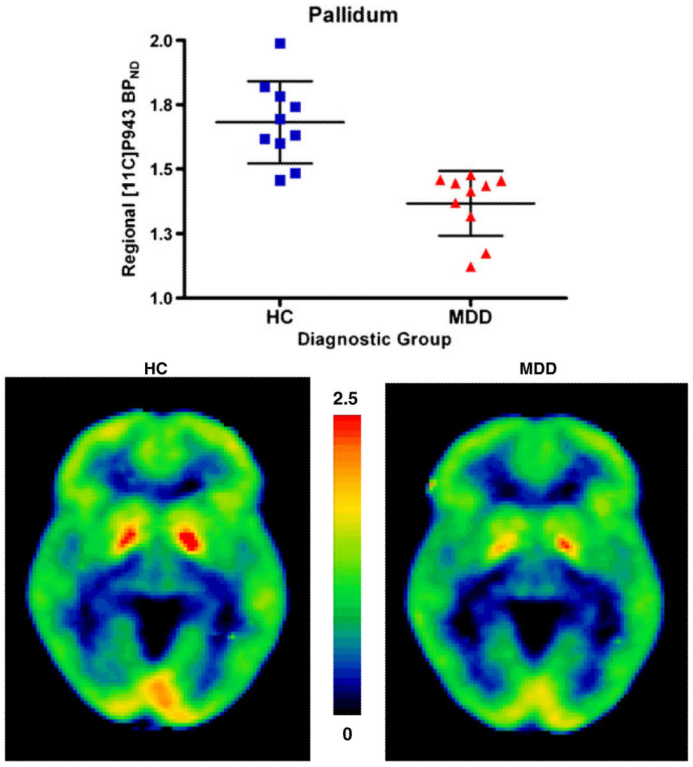

Fig. 1.

Upper panel: plot showing significant differences in ventral striatum/ventral pallidum (VS/VP) region of interest [^{11}C]P943 binding potential (BP_{ND}) between patients with major depressive disorder (*MDD*) and healthy control subjects (*HC*). *Lower panel*: average [^{11}C]P943 BP_{ND} co-registered positron emission tomography images illustrate reduced VS/VP [^{11}C]P943 BP_{ND} in MDD (*right*) relative to HC (*left*)

Table 1

Study participant demographic, clinical and positron emission tomography procedural characteristics

	Healthy control (*N*=10)	**Major depression (*N*=10)**	***P***
Age (years)	30.7±10.5	30.8±9.5	0.81
	Range: 19–49	Range: 20–45	–
Gender	5F, 5M	5F, 5M	1
Race	4AA, 1H, 5C	2AS, 1H, 7C	–
BMI	26.5±3.6	29.7±10.6	0.38
Smoking status	10N 7N,	3S	0.06
Age at first MDE (years)	–	16.5±2.1	–
Total No. of MDEs	–	5.6±4.3	–
Duration of current MDE (months)	–	9.4±5.3	–
		Range: 4–20	
Family history of MDD (%)	0	10 (100%)	–
MADRS score	4.6±3.0	23.9±5.0	<0.001
HAM-A score	3.2±3.0	13.9±5.5	<0.001
Injected dose (MBQ)	631.1±131	700.0±17.0	0.12
Specific activity (MBQ/nmol)	4.4±2.1	4.9±2.1	0.64
Injected mass (μg)	1.9±0.9	2.5±1.5	0.28

Data presented in mean±standard deviation, unless otherwise indicated. *P* values determined by independent sample *t* tests for continuous variables or by Chi-square for dichotomous variables

AA African-American, *AS* Asian-American, *BMI* body mass index, *C* Caucasian, *F* female, *H* Hispanic, *M* male, *MDD* major depressive disorder, *MDE* major depressive episode, *N* nonsmoker, *S* smoker