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Serotonin-1A receptor binding is positively associated with gray matter volume — A multimodal neuroimaging study combining PET and structural MRI

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ABSTRACT

Animal models revealed that the serotonin-1A (5-HT$_{1A}$) receptor modulates gray matter structure. However, there is a lack of evidence showing the relationship between 5-HT$_{1A}$ receptor concentration and gray matter in the human brain *in vivo*. Here, to demonstrate an association between the 5-HT$_{1A}$ receptor binding potential, an index for receptor concentration, and the local gray matter volume (GMV), an index for gray matter structure, we measured 35 healthy subjects with both positron emission tomography (PET) and structural magnetic resonance imaging (MRI). We found that regional heteroreceptor binding was positively associated with GMV in distinctive brain regions such as the hippocampi and the temporal cortices in both hemispheres (R^2 values ranged from 0.308 to 0.503, $p<0.05$ cluster-level FDR-corrected). Furthermore, autoreceptor binding in the midbrain raphe region was positively associated with GMV in forebrain projection sites ($R^2=0.656$, $p=0.001$). We also observed a broad range between 5-HT$_{1A}$ receptor binding and GMV. Given the congruence of altered 5-HT$_{1A}$ receptor concentrations and GMV reduction in depression or Alzheimer's disease as reported by numerous studies, these results might provide new insights towards understanding the mechanisms behind GMV alterations observed in these brain disorders.

Introduction

Growing evidence shows distinctive neuromodulatory properties of serotonin (5-hydroxytryptamine, 5-HT) in developing and mature brain networks (Daubert and Condron, 2010; Gaspar et al., 2003). Early alterations in the 5-HT system are associated with life-long changes in cognitive and behavioral functioning and the neuronal organization in neuropsychiatric diseases (Gaspar et al., 2003). The 5-HT$_{1A}$ receptor, one of at least 16 receptors in the serotonergic system, is directly linked to signaling cascades mediating neuroplasticity (Azmitia, 2001). Structural neuroimaging techniques revealed increased amounts of gray matter volume (GMV) as surrogate for enhanced neuroplasticity in relation to motoric training, cognitive performance or treatment with the antidepressant fluoxetine, a selective serotonin reuptake inhibitor (Draganski et al., 2004; Kanai and Rees, 2011; Vetencourt et al., 2008). On the other side, GMV loss as measured with high-resolution structural magnetic resonance imaging (MRI), is a key feature of neuropsychiatric brain disorders, whereby the hippocampal formation was demonstrated to be especially vulnerable to volumetric alterations (Benninghoff et al., 2010; Geuze et al., 2005).

Serotonin-1A autoreceptors are located presynaptically on serotonergic neurons in the raphe nuclei where they reduce tonic cell firing, thus autoinhibiting 5-HT release (Hall et al., 1997). Postsynaptically, 5-HT$_{1A}$ heteroreceptors are expressed on glutamatergic and GABAergic neurons and mediate an inhibitory serotonergic response (Amargós-Bosch et al., 2004; Hall et al., 1997; Puig et al., 2005). Neurobiological studies identified a vast number of second messenger pathways that exert neuroplastic changes (Citri and Malenka, 2008; Pittenger and Duman, 2008) triggered by 5-HT *via* 5-HT$_{1A}$ receptors (Azmitia, 2001; Tardito et al., 2006). To sum up, 5-HT$_{1A}$ receptors might be involved in altering GMV, thereby offering a possible explanation for gray matter atrophy observed in several brain disorders.

Dysfunctional neuronal organization is an important contributor to the pathogenesis of Alzheimer's disease (Mesulam, 1999), schizophrenia (Lewis and González-Burgos, 2008) and depressive disorder (Pittenger and Duman, 2008), however the underlying molecular mechanisms, leading to gray matter loss in these disorders are complex and not fully understood. Interestingly, positron emission

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tomography (PET) studies demonstrated alterations of 5-HT_{1A} receptors in patients suffering from these disorders (Kasper et al., 2002; Kepe et al., 2006; Lanzenberger et al., 2007; Mamo et al., 2007; Savitz et al., 2009). This congruence and a lack of data in human brains *in vivo* lead us to investigate the relationship between 5-HT_{1A} receptor concentration and GMV with a multimodal neuroimaging approach.

Material and methods

Participants

We examined 35 healthy adults, 18 males and 17 females (age range = 21–52, mean = 26.6 ± 6.8 years, Table 1), with at least general qualification for university entrance as lowest educational level. All subjects were recruited *via* advertisement at the Medical University of Vienna, Austria and underwent a general physical and neurological examination at the screening visit including medical history, electrocardiogram and routine laboratory tests. Inclusion criteria were age between 18 and 60, ability to perform study procedures and absence of any acute or chronic disease. Exclusion criteria comprised any history of severe disease, any psychiatric or neurologic disorder, previous drug abuse, pregnancy as assessed by urine pregnancy tests and any continuous medication for three months prior to the study. All participants provided written informed consent after written and oral presentation of a general intelligible information form and received reimbursement after participation. The institutional review board of the Medical University of Vienna, Austria, gave approval to all study procedures. The pooled study sample consisted of subjects who were part of PET and MRI studies previously published by our group (Hahn et al., 2010; Spindelegger et al., 2009).

Magnetic resonance imaging and image preprocessing

Structural magnetic resonance imaging was performed at the MR Center of Excellence at the Medical University of Vienna, Austria, with a 3 Tesla whole-body MEDSPEC S300 MR-scanner (Bruker BioSpin, Ettlingen, Germany) using a magnetization-prepared rapid gradient echo (MPRAGE, T1-weighted) sequence (128 slices, 256 × 256 matrix, slice thickness 1.56 mm, voxel size 0.78 × 0.86 mm). To optimize image-preprocessing quality we used the DARTEL (Diffeomorphic Anatomical Registration using Exponentiated Lie algebra) algorithm (Ashburner, 2007), which ranked top in a comparison of 14 image registration algorithms (Klein et al., 2009). The major advantage of the DARTEL algorithm is an increase in the accuracy of inter-subject alignment by a high number of parameters derived from deformation fields. T1-weighted images of all 35 subjects in our study were manually re-oriented and segmented using the *New Segment* option in SPM8 (2009, Wellcome Trust Centre for Neuroimaging, Institute of Neurology, University College London, London, United Kingdom, http://www.fil.ion.ucl.ac.uk/spm/software/spm8/) to generate rigid-body aligned gray matter, white matter and CSF-images. After segmentation all images were visually checked for major artifacts. The DARTEL algorithm consecutively generates six individual templates based on deformation fields calculated during segmentation, where the last template produced (number 6) was used for normalization. Each individual's segmented gray matter image together with each deformation field and the template was normalized to standard Montreal Neurological Institute (MNI) space at a voxel size of 1.5 × 1.5 × 1.5 mm. To correct for nonlinear spatial normalization, images were modulated by multiplication with the Jacobian determinants of the deformation fields in order to preserve the actual amount of gray matter within each structure before normalization. Based on this, the modulated images are further referred to as gray matter volume (GMV). The resultant values represent a quantitative measure of gray matter tissue volume per unit volume of the spatially normalized images (Ashburner and Friston, 2009). Finally, GMV images were smoothed with an 8-mm full-width at half-maximum Gaussian kernel. Such smoothing is considered sufficient to increase the stability of segmented images with respect to small registration errors.

Table 1
Demographic and radiochemical variables of study subjects.

	All subjects	Males	Females	*p*
n	35	17	18	
Age	26.6 ± 6.8	29.6 ± 8.4	24.4 ± 2.5	0.026^{+}
Weight (kg)	71.3 ± 14.6	79.7 ± 11.7	62.5 ± 12.2	<0.001
GMV (cm^3)	731.5 ± 73.8	777.5 ± 53.9	682.8 ± 58.5	<0.001
Injected dose (MBq)	385 ± 36	396.9 ± 45.8	372.3 ± 14.4	0.002^{+}
RCP (%)	97.7 ± 1.4	98 ± 1.4	97.4 ± 1.3	0.320

Data are given as means ± standard deviation. GMV = total gray matter volume, MBq = megabecquerel, RCP = radiochemical purity, *p* compares males and females with independent sample t-test or Mann–Whitney U test ($^{+}$) where normal distribution was not obtained by Levene's test.

Radiochemistry

The 5-HT_{1A} receptor specific radioligand [*carbonyl*-^{11}C]WAY-100635 was prepared at the Cyclotron Unit of the PET center at the Department of Nuclear Medicine of the Medical University of Vienna, Austria according to the optimized synthesis instruction proposed by Wadsak et al. (2007). [*Carbonyl*-^{11}C]WAY-100635 was prepared in a multistep radiosynthesis starting from cyclotron-produced [^{11}C]CO_2 and purified by high-performance liquid chromatography and solid-phase extraction. [*carbonyl*-^{11}C]WAY-100635 was dissolved in a phosphate-buffered saline solution and injected at a target dose of 5.4 MBq/kg bodyweight, further details of radiochemical variables are given in Table 1.

Positron emission tomography (PET) measurements

PET was performed at the Department of Nuclear Medicine of the Medical University of Vienna, Austria with a GE advance full-ring scanner (General Electric Medical Systems, Milwaukee, WI). Each subject's head was placed in the scanner parallel to the orbitomeatal line guided by a laser beam system to ensure full coverage of the neocortex and the cerebellum in the field of view (FOV). A polyurethane cushion and head straps kept the head in position to minimize head movement and to guarantee a soft head rest during the whole scanning period. Initially, a 5-minute transmission scan in two-dimensional mode was conducted to correct for tissue attenuation with a retractable ^{68}Ge ring source. Dynamic PET scans started simultaneously with the intravenous bolus injection of the radioligand [*Carbonyl*-^{11}C]WAY-100635. PET scans lasted for 90 min per subject and were acquired in a three-dimensional mode. The overall dynamic scan time was divided in 30 successive time frames (15 × 1 min, 15 × 5 min). The emission data were scatter- and attenuation corrected based on the data from the transmission scans and reconstructed using an iterative filtered back-projection algorithm (FORE + ITER). The final spatial resolution of the reconstructed volume was 4.36 mm full-width at half maximum at the center of the FOV. We did not perform realignment for head movement upon visual inspection of PET-data quality. All 30 dynamic PET image frames were summed (PET_{ADD}) for co-registration to the MRI.

Quantification of 5-HT_{1A} receptor binding potential

We assessed *in vivo* receptor density as indexed by 5-HT_{1A} receptor binding potential (BP_{ND}), the ratio at equilibrium of specifically bound radioligand to that of nondisplaceable radioligand in tissue (Innis et al., 2007). Binding was computed using the voxel-wise modeling tool in the PMOD software package (v3.1, 2009, for Linux,