Probing the association between serotonin-1A autoreceptor binding and amygdala reactivity in healthy volunteers

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ABSTRACT

Introduction: The serotonergic system modulates affect and is a target in the treatment of mood disorders. 5-HT1A autoreceptors in the raphe control serotonin release by means of negative feedback inhibition. Hence, 5-HT1A autoreceptor function should influence the serotonergic regulation of emotional reactivity in limbic regions. Previous findings suggest an inverse relationship between 5-HT1A autoreceptor binding and amygdala reactivity to facial emotional expressions. The aim of the current multimodal neuroimaging study was to replicate the previous finding in a larger cohort.

Methods: 31 healthy participants underwent fMRI as well as PET using the radioligand \(\text{[carbonyl]}^{11}\text{C} \text{WAY-100635}\) to quantify 5-HT1A autoreceptor binding in the dorsal raphe. The binding potential (BPND) was quantified using the multilinear reference tissue model (MRTM2) and cerebellar white matter as reference tissue. Functional MRI was done at 3T using a well-established facial emotion discrimination task (EDT). Here, participants had to match the emotional valence of facial expressions, while in a control condition they had to match geometric shapes. Effects of 5-HT1A autoreceptor binding on amygdala reactivity were investigated using linear regression analysis with SPM8.

Results: Regression analysis between 5-HT1A autoreceptor binding and mean amygdala reactivity revealed no statistically significant associations. Investigating amygdala reactivity in a voxel-wise approach revealed a positive association in the right amygdala (peak-T = 3.64, p < .05 FWE corrected for the amygdala volume) which was however conditional on the omission of age and sex as covariates in the model.

Conclusion: Despite highly significant amygdala reactivity to facial emotional expressions, we were unable to replicate the inverse relationship between 5-HT1A autoreceptor binding in the DRN and amygdala reactivity. Our results oppose previous multimodal imaging studies but seem to be in line with recent animal research. Deviation in results may be explained by methodological differences between our and previous multimodal studies.

Introduction

Serotonin is one of the oldest transmitting chemicals in living organisms. Although in mammals serotonin has been detected in nearly all tissues of the body, its role as neurotransmitter has been of immense interest since discovery in 1937 (Muller and Jacobs, 2010). Within the realm of neuroscience and psychiatry, many researchers have focused on the serotonergic system's modulatory role in affect and mood. Powerful support for this role comes from the fact that selective serotonin reuptake inhibitors (SSRIs) are an effective treatment for mood disorders. Using positron emission tomography (PET) and suitable radioligands it is possible to quantify serotonergic receptors and

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transmitters in healthy and diseased states. Human studies indicate alterations in 5-HT1A receptor function in psychiatric disorders showing decreased binding in patients with anxiety (Lanzenberger et al., 2007) and depression (Drevets et al., 2007) although some studies also suggest increased binding (Parsey et al., 2005, 2010, 2006). The 5-HT1A receptor exists as heteroreceptor in projection areas and as autoreceptor in serotonergic raphe nuclei. As heteroreceptor 5-HT1A receptors mediate the serotonergic influence on affective and cognitive processing in projection sites whereas as autoreceptor it controls serotonergic raphe cell-firing by means of feedback inhibition (Pineyro and Blier, 1999).

The dorsal raphe nucleus (DRN), one of the two rostral serotonergic nuclei projecting to the forebrain, has dense projections to the amygdala (Vertes, 1991). Various lines of evidence including brain lesion studies, nuclei projecting to the forebrain, has dense projections to the amygdala verse relationship between 5-HT1A autoreceptor binding in the DRN and using PET and functional MRI, Fisher et al. (2006) demonstrated an in-tivity in the amygdala in humans. In an in further and investigated a serotonergic modulation of emotional reac-tivity in serotonergic raphe cell bodies (Pusar-Poli et al., 2009). Interestingly, also the DRN seems to process the entirety of the valence spectrum including negative as well as positive aspects, e.g. rewards (Hayashi et al., 2015; Nakamura et al., 2008) or emotional behaviors (Teissier et al., 2015; Urban et al., 2016).

Several animal studies indicate a causal effect of serotonergic midbrain projections on affective processing of the amygdala (Marcin-kiewcz et al., 2016; Sengupta et al., 2017). Few studies went a step further and investigated a serotonergic modulation of emotional reactivity in the amygdala in humans. In an influential multimodal paper using PET and functional MRI, Fisher et al. (2006) demonstrated an inverse relationship between 5-HT1A autoreceptor binding in the DRN and bilateral amygdala reactivity to fearful and angry facial expressions in 20 healthy volunteers indicating increased serotonin release associated with increased amygdala reactivity. This inverse relationship was recently replicated albeit in a small sample of n = 15 and only for the left amygdala (Selvaraj et al., 2015).

To further elucidate a potential link between serotonin-1A autoreceptor binding and amygdala reactivity to emotional faces, the aim of the current multimodal neuroimaging study was to replicate the previous findings in a larger cohort of n = 31 using an fMRI sequence optimized to assess amygdala activation.

Materials and methods

Subjects

A total of 31 healthy participants (aged 26.5 ± 4.8 years, 18 female) were included in this study, taken from samples of which data have been published previously (Fink et al., 2009; Hahn et al., 2010, 2011, 2012; Lanzenberger et al., 2007; Stein et al., 2008). PET data of 36 participants were available (Hahn et al., 2010) but only 31 of them also underwent fMRI scanning. Participants underwent the Structured Clinical Interview (SCID) of the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV), standard medical examinations, routine laboratory tests, and an electrocardiogram to rule out physical, neurological and psychiatric disorders. Further exclusion criteria were past or current substance abuse, recent intake of psychotropic medication, implants or steel grafts, pregnancy (tested with a urine human chorionic gonadotropin pregnancy test at the screening visit and before the fMRI and PET scans), hormonal treatment, and intake of oral contraceptives. Participants provided written informed consent after detailed explanation of the study protocol and received reimbursement for their participation. The study was approved by the Ethics Committee of the Medical University of Vienna and was performed according to the Declaration of Helsinki.

Positron emission tomography

Each participant underwent a PET scan which was carried out with a GE Advance scanner (General Electric Medical Systems), at the Department of Biomedical Imaging and Image-guided Therapy, Division of Nuclear Medicine, Medical University of Vienna. 5-HT1A receptor binding was quantified using the radioligand [carbonyl-11C]WAY-100635, see Wadsak et al. (2007) for synthesis. After a 5-min tissue attenuation scan (retract-able 68Ge rod sources) a 3D dynamic emission measurement and syn-chronous injection of the radioligand followed and lasted for 90 min (30 frames: 15 × 1 min, 15 × 5 min). Reconstructed images comprised a spatial resolution of 4.36 mm full-width at half-maximum at the center of the field of view (matrix 128 × 128, 35 slices). PET scans were corrected for head motion (each frame was realigned to the mean image and in a second pass to the motion corrected mean image) and normalized to MNI space using SPM8 with default settings for remaining parameters (Wellcome Trust Center for Neuroimaging; http://www.fil.ion.ucl.ac.uk/spm). To ensure optimal spatial overlap between PET and fMRI image modalities, the normalization was carried out via the corresponding T1-weighted MRI. Hence, structural MRI scans were normalized using the standard seg-mentation option of SPM8, and the obtained transformation matrix was applied to the coregistered PET frames (Hahn et al., 2012).

Quantification of 5-HT1A receptor binding potential

Quantification of the 5-HT1A receptor binding potential BPND (Finnis et al., 2007) was done in PMOD 4.3 (PMOD Technologies) using the multilinear reference tissue model, MRTM2 (Ichise et al., 2003) with cerebellar white matter as reference tissue (Hirvon et al., 2007; Parsey et al., 2005, 2010). Here, k’γ was calculated from the insula and cerebellar white as receptor-rich and -poor regions, respectively (Hahn et al., 2010). The DRN region of interest (ROI; 4 mm diameter) was defined manually in two slices of the original (non-normalized) summed PET image according to (Hahn et al., 2010, 2012; Kranz et al., 2012). Correct ROI location was ensured using the coregistered magnetic resonance imaging scan. Voxel-wise 5-HT1A maps within an amygdala mask were defined by the Harvard Oxford atlas.

Functional magnetic resonance imaging

In addition to PET, each participant underwent a structural and func-tional MRI measurement in a 3 Tesla Medspec S300 (Bruker Biospin) scanner (within one week after the PET measurement). To specifically assess neuronal activation of the amygdala, an optimized MRI sequence was employed (Robinson et al., 2004; Windischberger et al., 2010). Briefly, a single-shot gradient-recalled echo-planar imaging sequence was used [echo time (TE) = 31 ms, repetition time (TR) = 1000 ms] yielding 10 axial slices aligned to the anterior commissure-posterior commissure (AC-PC) line (3-mm thickness + 0.5 mm slice gap). Standard preprocessing included correction for slice-timing differences and head motion, normalization to MNI space, and spatial smoothing with a Gaussian kernel of 9 mm, resulting in a final voxel size of 2 × 2 × 2 mm. Standard pre-processing was carried out in SPM8 using default parameters. In order to elicit amygdala reactivity, a well-established facial emotion discrimination task (EDT) was used based on Hariri et al. (2002). Here, participants had to match the emotional valence of three facial expressions (‘faces’), while in a control condition they had to match geometric shapes (‘objects’). Trial duration depended on the subject’s response time (max. 4s) and trials were presented in alternating blocks (5 × 20s faces and 5 × 20s objects) with 20s baseline blocks depicting a white crosshair placed on a black back-ground in between task blocks (Hahn et al., 2011). Face stimuli were taken from the NimStim set of facial expressions including anger, disgust, fear, happiness, sadness, surprise, or calmness (Tottenham et al., 2009). Facial expressions were randomly dispersed across blocks. Mean and voxel-wise activation associated with face matching (Face > Object) was calculated within an amygdala mask as defined by the Harvard Oxford atlas. The
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