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Diurnal and seasonal variation of the brain serotonin system in healthy male subjects

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ABSTRACT

The mammalian circadian clock underlies both diurnal and seasonal changes in physiology, and its function is thought to be disturbed in both seasonal and non-seasonal depression. In humans, molecular imaging studies have reported seasonal changes in the serotonin system. Despite the role of the circadian clock in generating seasonal physiological changes, however, diurnal variation of serotonin receptors and transporters has never been directly studied in humans. We used positron emission tomography to examine diurnal and seasonal changes in the serotonin 5-HT_{1A} receptor and serotonin transporter in two large cohorts of healthy male subjects, employing a cross-sectional design. In 56 subjects measured with [^{11}C]WAY-100635, we observed diurnal increases in the availability of 5-HT_{1A} receptors in the cortex. In 40 subjects measured with [^{11}C]MADAM, a decrease in 5-HTT was observed in the midbrain across the day. We also found seasonal changes in the 5-HT_{1A} receptor in serotonin projection regions, with higher availability on days with a longer duration of daylight. Our observation that serotonin receptor and transporter levels may change across the day in humans is corroborated by experimental research in rodents. These findings have important implications for understanding the relationship between the circadian and serotonin systems in both the healthy brain and in affective disorders, as well as for the design of future molecular imaging studies.

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Introduction

Circadian rhythms are instrumental to the health and survival of animals and plants, as they allow for the physiological anticipation of regular 24 hour day–night cycles. In mammals, circadian rhythms are synchronised by the suprachiasmatic nucleus (SCN) within the hypothalamus, which functions as the master circadian pacemaker (Dibner et al., 2010; Duffy and Czeisler, 2009; Reppert and Weaver, 2002). By its entrainment to the natural rhythms of sunrise and sunset, the circadian clock encodes day length (VanderLeest et al., 2007; Wehr et al., 2001; Wright et al., 2013). In this way, the circadian clock also functions as a circannual clock, driving seasonal changes in physiology (Dardente et al., 2010; Sumova et al., 1995).

Seasonal affective disorder (SAD) is a form of depression which recurs in the winter months (Rosenthal et al., 1984). This condition has been shown to have a circadian basis, arising from seasonal changes in day length: insufficient daytime light is thought to lead to a shift in the phase of melatonin secretion rhythms (Levitan, 2007). Disruptions in chronobiology have also been proposed to play an important role in non-seasonal major depressive disorder (MDD) (Wirz-Justice, 2006), and it was recently observed that circadian patterns of gene expression are disturbed in the brains of patients with this condition (Li et al., 2013). Correspondingly, bright light- and melatonin-based chronotherapeutics have been successfully applied to both SAD and MDD (Golden et al., 2005; Hickie and Rogers, 2011; Lewy et al., 2006). The mechanisms by which circadian disturbances may lead to depressive symptoms, however, are poorly understood.

At the level of neurotransmission, the serotonin system has attracted particular interest in relation to the regulation of circadian rhythms (Ciarleglio et al., 2011; Morin, 1999). Serotonin is an indoleamine closely related to melatonin. In rodents, brain serotonin levels change across the day, entrained to light onset and offset (Birkett and Fite, 2005; Cagampang et al., 1993; Wesemann et al., 1986). In humans, early post-mortem studies have demonstrated a marked circadian as well as seasonal variation of serotonin concentration in several brain regions (Bucht et al., 1981; Carlsson et al., 1980; Wesemann et al., 1986).

Positron Emission Tomography (PET) allows for in vivo quantification of proteins within the brain. Using this technique, the availability of the serotonin transporter (5-HTT) and 5-HT_{1A} receptor subtype

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have been shown to vary across seasons, specifically in relation to changes in environmental light (Kalbitzer et al., 2010; Praschak-Rieder et al., 2008; Spindelegger et al., 2012). Despite the central role of the circadian clock in generating seasonal changes in physiology, changes in the levels of serotonin receptors and transporters across the day have, to our knowledge, not been examined in human subjects.

The aim of the present study was to examine changes in the human brain 5-HT system in relation to rhythmic patterns of light exposure, extending previous seasonal findings to include diurnal variation for the first time. The relationships were investigated in control subjects examined using PET and the radioligands [^{11}C]WAY-100635 and [^{11}C]MADAM to measure the availability of the 5-HT$_{1A}$ receptor and the 5-HTT respectively.

Materials and methods

Subjects

All subjects participated as control subjects in studies using the same PET system. In all studies, subjects underwent physical and mental health examinations prior to participation and were deemed to be physically healthy and showing no history of significant psychiatric or somatic illness. PET images were analysed in a homogeneous manner allowing for pooling of the data. In total, this database includes sixty nine subjects (13 females, 56 males) examined using [^{11}C]WAY-100635, and forty eight subjects (8 females, 40 males) examined using [^{11}C]MADAM. These numbers are calculated after the exclusion of three [^{11}C]WAY-100635 measurements and one [^{11}C]MADAM measurement for technical reasons such as image artefacts and coregistration failure. Of the subjects examined with [^{11}C]WAY-100635, there were 9 pairs of monozygotic twins and 10 pairs of dizygotic twins.

Female subjects were not included in the analyses since gender and gonadal hormones have been shown to influence sleep and circadian function (Mong et al., 2011) as well as the availability of 5-HT$_{1A}$ receptors and 5-HTTs (Jovanovic et al., 2009).

The studies were approved by the Regional Ethics Committee in Stockholm and the Radiation Safety Committee of the Karolinska Hospital, and all subjects provided written informed consent prior to their participation in the studies.

MRI procedure

MRI images were acquired using a 1.5T GE Signa system (Milwaukee, WI). T1- and T2-weighted MRI images were acquired for all subjects. T2-weighted images were examined for structural pathology as a criterion for subject inclusion. The T1-weighted images were used for all further data processing and delineation of regions of interest (ROIs).

Radiosynthesis and PET experimental procedure

To minimise head movement, a plaster helmet was made for each subject and employed during the PET measurements. All PET measurements were conducted with an ECAT Exact HR 47 system (CTI/Siemens, Knoxville, TN) run in 3D mode. Spatial resolution ranges from 3.6 mm full width half maximum (FWHM) at the centre of the field to 4.5 mm tangentially and 7.4 mm radially at 20 cm from the centre (Wienhard et al., 1994). Prior to each PET measurement, transmission scans were performed using three rotating ^{68}Ge rods in order to correct for signal attenuation.

[^{11}C]WAY-100635 was synthesized as described previously (Hall et al., 1997). After i.v. injection of [^{11}C]WAY-100635, radioactivity in brain was measured for 69 min in a consecutive series of 16 frames of lengths 3 × 60, 4 × 180 and 9 × 360 s. [^{11}C]MADAM was synthesized as described previously (Tarkiainen et al., 2001). After injection, radioactivity was measured for 93 min. For 33 of the subjects, the acquisition was binned into 20 time frames of lengths 3 × 60, 4 × 180 and 13 × 360 s, and for the remaining 6 subjects, the frame timing was 4 × 15, 4 × 30, 6 × 60, 6 × 180, and 11 × 360 s. Following correction for attenuation, random and scattered events, images were reconstructed using filtered back projection, with a Hann filter of 2 mm cut off frequency. The reconstructed volume was displayed as 47 horizontal sections with a voxel size of 2.02 × 2.02 × 3.125 mm^3.

Image preprocessing

PET images were corrected for residual head motion by using a post-reconstruction frame-by-frame realignment algorithm in which all frames were individually realigned to the first minute of acquisition. The realignment calculations were performed within SPM5 (Wellcome Department of Cognitive Neurology, University College London). MR images were reoriented into the AC-PC plane, and subsequently segmented into grey matter, white matter and cerebrospinal fluid, and coregistered to PET images using SPM5.

Region of interest (ROI) delineation

Cortical and subcortical ROIs were delineated using Freesurfer (version 5.0.0, http://surfer.nmr.mgh.harvard.edu/). Previous PET investigations examining changes in binding to the 5-HT$_{1A}$ receptor (Spindelegger et al., 2012) and the 5-HTT (Kalbitzer et al., 2010; Praschak-Rieder et al., 2008) with light and season respectively have reported relatively homogeneous effects in serotonin projection regions. For this reason, and because preclinical studies have not reported any regional specificity of diurnal changes in projection regions (Akiyoshi et al., 1989; Lu and Nagayama, 1997), we examined large ROIs comprised of sets of smaller regions which were themselves based on the findings of previous papers. For [^{11}C]WAY-100635, this included a cortical ROI (consisting of the frontal, temporal, insular and cingulate cortices) and a subcortical ROI (consisting of the amygdala and hippocampus). For [^{11}C]MADAM, this included a striatal ROI (consisting of caudate, putamen and ventral striatum) and an extrastriatal ROI (consisting of the thalamus, hippocampus and amygdala).

For both radioligands, a ROI was defined for the dorsal raphe nucleus using parametric PET images, quantified using wavelet-assisted parametric imaging (WAPI) in order to reduce noise in small regions. The delineation was performed according to a recently described method (Schain et al., 2013), guided by midbrain anatomy (Kranz et al., 2012). This ROI was defined by the inclusion of the four voxels (of 12.8 mm^3 each) of greatest intensity. Thus, this volume corresponds closely with the reported volume of 42.2 mm^3 for this region in control subjects post-mortem (Arango et al., 2001).

A cerebellar reference region was delineated manually on the MR image for each subject individually using the Human Brain Atlas software. Manual delineation was performed to obtain optimal precision between individuals for this region being fundamental for quantitative analysis. The cerebellar ROI was drawn such that it included the cerebellar cortices and excluded the vermis, and such that it did not come any closer than twice the FWHM from the surfaces of the cerebellar cortices bordering occipital and temporal cortices. Furthermore because of the diminished signal-to-noise ratio of PET data in the most dorsal and ventral slices, the lowermost planes were not included in the cerebellar ROI. The ROI was delineated such that it also included cerebellar white matter of the cerebellar cortices. The grey and white matter segmentation obtained from the segmentation of the MRI was utilised to automatically divide the cerebellar ROI into separate grey and white matter cerebellar regions.

Quantitative analysis

The regional binding potential (BP$_{ND}$) values were calculated using the simplified reference tissue model (SRTM). SRTM has been validated for [^{11}C]WAY-100635 (Gunn et al., 1998) and [^{11}C]MADAM binding

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