Psychiatry Research: Neuroimaging 212 (2013) 125–131

Contents lists available at SciVerse ScienceDirect

Psychiatry Research: Neuroimaging

journal homepage: www.elsevier.com/locate/psychresns

Trait aggression and trait impulsivity are not related to frontal cortex 5-HT2A receptor binding in healthy individuals

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ARTICLE INFO

Article history:
Received 3 May 2012
Received in revised form
6 July 2012
Accepted 11 September 2012

Keywords:
Aggression
Impulsivity
Serotonin
Positron Emission Tomography (PET)

ABSTRACT

Numerous studies indicate that the serotonergic (5-HT) transmitter system is involved in the regulation of impulsive aggression and there is from post-mortem, in vivo imaging and genetic studies evidence that the 5-HT2A receptor may be involved. We investigated 94 healthy individuals (60 men, mean age 47.0 ± 18.7, range 23–86) to determine if trait aggression and trait impulsivity were related to frontal cortex 5-HT2A receptor binding (5-HT2AR) as measured with [^{18}F]-altanserin PET imaging. Trait aggression and trait impulsivity were assessed with the Buss–Perry Aggression Questionnaire (AQ) and the Barratt Impulsiveness Scale 11 (BIS-11). Statistical analyses were conducted using a multiple linear regression model and internal consistency reliability of the AQ and BIS-11 was evaluated by Cronbach's alpha. Contrary to our hypothesis, results revealed no significant associations between 5-HT2AR and the AQ or BIS-11 total scores. Also, there was no significant interaction between gender and frontal cortex 5-HT2AR in predicting trait aggression and trait impulsivity. This is the first study to examine how 5-HT2AR relates to trait aggression and trait impulsivity in a large sample of healthy individuals. Our findings are not supportive of a selective role for 5-HT2AR in mediating the 5-HT related effects on aggression and impulsivity in psychiatrically healthy individuals.

1. Introduction

Violence has a substantial impact on our society, accounting for an estimated 1.6 million deaths worldwide annually (Krug et al., 2002). Aggression plays a critical role in the manifestation of violence and criminality, and given the extensive morbidity of this behaviour there is a need for a better understanding of the underlying neurobiological mechanisms. Aggression is most commonly divided into impulsive and premeditated subtypes (Barratt et al., 1999), referring to unplanned or reactive acts of aggression and controlled or proactive acts of aggression, respectively.

There is abundant evidence that the 5-HT transmitter system plays a role in the modulation of aggressive behaviour (Siever, 2008), with most studies pointing to an inverse relationship between 5-HT and aggression, in particular impulsive aggression. A meta-analytic review of animal studies using 5-HT reuptake inhibitors (SSRIs), established an inhibitory effect of increased 5-HT levels on aggression (Carrillo et al., 2009). These preclinical findings have to some extent been corroborated in humans, where SSRIs are reported to reduce impulsive aggression in healthy subjects high in aggression scores (Berman et al., 2009) and in personality-disordered individuals with impulsive aggression (Coccaro and Kavoussi, 1997).

The neural circuits that regulate impulsive aggression involve the prefrontal cortex, a region of importance for modulating behavioural responses elicited by subcortical structures such as the amygdala (Siever, 2008). Evidence for the involvement of the prefrontal cortex comes from patients with brain lesions in this region, as they display heightened levels of aggression (Anderson et al., 1999; Grafman et al., 1996). According to prevailing theory, lowered levels of extracellular 5-HT in the prefrontal cortex underlie individual differences in aggression and behavioural disinhibition (Davidson et al., 2000; New et al., 2009; Siever, 2008). For example, in an acute tryptophan depletion (ATD) study, connectivity within the prefrontal cortex–amygdala circuits was modulated by ATD when processing angry faces (Passamonti et al., 2011).

There are several lines of evidence supporting that the serotonin 2A (5-HT2A) receptor is involved in aggression. Numerous

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http://dx.doi.org/10.1016/j.pscychresns.2012.09.007

studies have convincingly shown that pharmacological compounds that antagonise 5-HT2A/C receptors potently suppress the display of aggressive behaviour in various animal species, including humans (reviewed in; (de Boer and Koolhaas, 2005). Furthermore, specific genetic polymorphisms of the 5-HT2A receptor are associated with aggression (Giegling et al., 2006; Nomura and Nomura, 2006), although it still remains to be determined if these polymorphisms affect 5-HT2A receptor at protein levels. A post-mortem study has shown that 5-HT2A receptor expression in the prefrontal cortex is positively correlated with lifetime aggression in subjects who committed suicide, but not in subjects who died from non-neurological causes (Oquendo et al., 2006). Finally, two PET-studies have reported that frontal cortex 5-HT2A receptor binding (5-HT2AR) is higher in physically aggressive patients with personality disorders who scored high on a state measure of impulsive aggression (Rosell et al., 2010), and in patients with borderline personality disorder (Soloff et al., 2007) as compared to healthy controls.

In the present study we investigated in a large group of healthy individuals whether trait aggression and trait impulsivity are associated with frontal cortex 5-HT2AR as measured with in vivo brain imaging. Based on the findings in previous studies that 5-HT2AR are increased in clinical populations with heightened levels of aggression, we hypothesised that (1) trait aggression and trait impulsivity in *healthy* subjects are associated with increased frontal cortical 5-HT2AR and that (2) inter-individual variations in regional receptor binding cause variability in behavioural outcomes.

2. Methods

2.1. Subjects

Ninety-four subjects, 60 men and 34 women, with a mean age of 47.0 ($\pm$ 18.7, range 23–86) years, were included in the study as a subset of healthy volunteers who underwent 5-HT2A receptor imaging using [^{18}F]altanserin - positron emission tomography (PET) in the period from 2000 to 2008. The participants were recruited through advertisement, and all signed an informed consent. The study was approved by the Ethics Committee of Copenhagen, Denmark and was conducted in accordance with the Declaration of Helsinki. Subjects were interviewed by the investigator for assessment of medical history. None of the subjects had a history of present or prior neurological or psychiatric disease, nor were any of the subjects taking psychoactive drugs. All subjects had a body mass index (BMI) <30, a normal neurological examination and their brain magnetic resonance image (MRI) was unremarkable.

Subsets of the cohort have been included in earlier reports on normative 5-HT2AR data (Adams et al., 2004), its relationship to neuroticism (Frokjaer et al., 2008), familial risk for mood disorder (Frokjaer et al., 2010b) and BMI (Erritzoe et al., 2009).

2.2. Aggression, impulsivity and personality assessment

The Buss–Perry Aggression Questionnaire (BPAQ) (Buss and Perry, 1992) and the Barratt Impulsiveness Scale version 11 (BIS-11) (Patton et al., 1995) were used to assess aggression and impulsivity. The BPAQ is a 29-item self-report measure scored on a 5-point Likert scale from (1) extremely uncharacteristic of me to (5) extremely characteristic of me. It consists of four aggression subscales: physical aggression, verbal aggression, anger and hostility, and provides a total score which can be used as a measure of trait aggressiveness.

The BIS-11 is 30-item self-report measure scored on a 4-point Likert scale from (1) rarely/never to (4) almost always/always. It consists of the three subscales: motor impulsiveness, attentional impulsiveness, and non-planning impulsiveness and like the BPAQ, the BIS-11 also provides a total score indicating a global measure of impulsivity.

These scales are internationally widely used and well-validated (Harris, 1997; Stanford et al., 2009), but have not previously been available in Danish. Therefore, the original English versions of the scales were translated into Danish by the investigators and a professional English translator. The original versions and the back-translations were then compared and the Danish version adjusted accordingly. Previously scanned participants were invited to fill in the questionnaires electronically. There was an interval of 2–10 years interval between the imaging sessions and acquisition of the aggression and impulsivity trait measures.

In addition, all subjects had also completed the Danish version of the 240-item NEO Personality Inventory-Revised (NEO PI-R) on the day of PET scan, measuring the personality dimensions Neuroticism, Extraversion, Openness, Agreeableness and Conscientiousness. The Danish translation of the NEO PI-R has been psychometrically evaluated and standardized in a sample of 600 subjects (Hansen et al., 2004).

2.3. Education

Education was assessed using an education score of 1–5, where 1 represents a work requiring no education, 2 represents a special worker (special training demanded), 3 represents a skilled worker (education of 4 years duration, mainly practical), 4 represents longer theoretical education (education of 4 years duration, mainly theoretical) and 5 represents an academic (education from university).

2.4. Imaging

5-HT2AR was imaged with [^{18}F]altanserin-PET according to Pinborg et al. (2003). PET scans were acquired in steady-state conditions with an 18-ring GE-Advance scanner. Acquisition procedures, reconstruction and quantification are described in detail elsewhere (Pinborg et al., 2003). The outcome parameter for [^{18}F]altanserin binding was the binding potential of specific tracer binding (BPp), defined as:

$$\mathrm{BPp} = [(C_{\mathrm{voi}} - C_{\mathrm{reference}})/C_{\mathrm{plasma}}] = f_{\mathrm{p}}\,(B_{\max}/Kd)\ \ (\mathrm{mL/mL}),$$

where C_{voi} and $C_{\mathrm{reference}}$ are steady state mean count densities in the volume of interest and in the reference region, respectively. C_{plasma} is the steady state activity of non-metabolized tracer in plasma, f_{p} is the free fraction of radiotracer in plasma, $B_{\max}$ is the density of receptor sites available for tracer binding, and Kd is the affinity constant of the radiotracer to the receptor.

Structural brain imaging with MRI was conducted in all subjects; magnetization-prepared rapid acquisition gradient echo (MP-RAGE) sequences were acquired on either a 1.5T Siemens Magnetom Vision scanner ($n=41$) or a 3T Siemens Magnetom Trio scanner ($n=53$). PET and MR images were co-registered through manual translation and rotation of the PET image with subsequent visual inspection in three planes, with a Matlab based programme (Mathworks Inc. Natick, MA) as described in Adams et al. (2004).

Volumes of interest were delineated in a strictly user-independent fashion according to Svarer et al. (2005). This method uses a volume of interest (VOIs) probability map based on a template set of 10 MRIs, where VOIs have been defined manually. After alignment, the VOIs were transferred onto the PET images. The frontal cortex served as the primary region of interest and consisted of a volume-weighted average of the orbitofrontal, anterior cingulate, superior frontal and medial inferior frontal cortices. The cerebellum was defined and used for non-specific