



Serotonin 2A receptor, serotonin transporter and dopamine transporter alterations in dogs with compulsive behaviour as a promising model for human obsessive-compulsive disorder

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ABSTRACT

Neuro-imaging studies have shown altered, yet often inconsistent, serotonergic and dopaminergic neurotransmission in patients with obsessive-compulsive disorder (OCD). We investigated both serotonergic and dopaminergic neurotransmission in 9 drug-naïve dogs with compulsive behaviour, as a potential model for human OCD. Single photon emission computed tomography was used with ¹²³I-R91150 and ¹²³I-FP-CIT, in combination with ^{99m}Tc-ECD brain perfusion co-registration, to measure the serotonin (5-HT) 2A receptor, dopamine transporter (DAT) and serotonin transporter (SERT) availability. Fifteen normally behaving dogs were used as reference group. Significantly lower 5-HT_{2A} receptor radioligand availability in frontal and temporal cortices (bilateral) was observed. Further, in 78% of the compulsive dogs abnormal DAT ratios in left and right striatum were demonstrated. Interestingly, both increased and decreased DAT ratios were observed. Finally, significantly lower subcortical perfusion and (hypo) thalamic SERT availability were observed in the compulsive dogs. This study provides evidence for imbalanced serotonergic and dopaminergic pathways in the pathophysiology of compulsions in dogs. The similarities with the altered neurotransmission in human OCD provide construct validity for this non-induced, natural canine model, suggesting its usefulness for future investigations of the pathophysiology of human OCD as well as the effectiveness of psychopharmacological interventions.

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1. Introduction

Obsessive-compulsive disorder (OCD) is a highly prevalent (2–3%) and chronic human illness characterised by the presence of recurrent, persistent and unwanted thoughts (obsessions) resulting in distress. In order to reduce this distress, repetitive, ritualistic acts (compulsions) are performed (American Psychiatric Association, 2000; Kessler et al., 2005).

The neurocircuitry of OCD is primarily located in the cortico-striatal-thalamic-cortical loops, including the orbitofrontal cortex (OFC), dorsolateral prefrontal cortex (DLPFC), anterior cingulate cortex (ACC), striatum and thalamus (Stein, 2002; Maia et al., 2008). The complementary involvement of other brain areas such as the amygdala have been suggested more recently (Friedlander and Desrocher, 2006; Menzies et al., 2008). All these regions are densely innervated by the serotonergic and dopaminergic neurotransmitter systems and both

systems are presumably involved in OCD (Westenberg et al., 2007). The involvement of the serotonergic (5-HT) system is mainly based on the successful pharmacological treatment of OCD with serotonin reuptake inhibitors (e.g. fluoxetine, clomipramine). More recent studies also suggest a role for the dopaminergic system in the pathophysiology of OCD (Denys et al., 2004b).

What strikes one most when analysing the *in vivo* neuroimaging results in humans with OCD is their highly inconclusive and often discrepant characteristic (Nikolaus et al., 2009). Reports concerning the 5-HT_{2A} receptor are still limited with one study describing a higher binding in the caudate nuclei and no cortical changes (Adams et al., 2005) whereas the other provides evidence for normal values for the caudate nuclei and a lower binding in multiple cortical areas (Perani et al., 2008). For the serotonin transporter (SERT) as well no consensus exists with reports mentioning elevations, no alterations as well as decreases of SERT bindings, even though a lower SERT availability is most often described (Pogarell et al., 2003; Stengler-Wenzke et al., 2004; van der Wee et al., 2004; Hesse et al., 2005; Hasselbalch et al., 2007; Reimold et al., 2007; Zitterl et al., 2007; Zitterl et al., 2008). The

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dopamine transporter (DAT) studies using ^{123}I - β -CIT also provide controversy in OCD with higher and lower DAT ratios reported (van der Wee et al., 2004; Hesse et al., 2005). Finally, next to discrepant neurotransmitter data, human OCD shows frontocortical perfusion alterations, next to regional cerebral blood flow (rCBF) alterations in the basal ganglia and cerebellum. These perfusion data remain complex to interpret due to the discrepancies of the results (normal, increased or decreased rCBF) (Swedo et al., 1989; Machlin et al., 1991; Rubin et al., 1992; Edmonstone et al., 1994; Lucey et al., 1997; Moriarty et al., 1997; Crespo-Facorro et al., 1999; Busatto et al., 2000; Alptekin et al., 2001; Topcuoglu et al., 2005). These conflicting results seriously hamper the neurobiological understanding of OCD, and demonstrate the urge of other research resources, such as animal models, to unravel the exact role of 5-HT and dopamine in this disease.

Abnormal repetitive motor behaviours are well-described in many animals like rodents, horses, pigs, cats or dogs (Cronin et al., 1985; Luescher, 2003; Meers and Odberg, 2005) and can occur spontaneously but are mostly induced in the laboratory for translational study purposes. In this study, we used dogs with non-pharmacologically induced compulsive behaviour, which is a similar approach to other research groups successfully using deer mice and rabbits as natural, spontaneous animal models of OCD (Korff et al., 2008, 2009; Hoffman and Rueda Morales, 2009). For instance, Korff et al. were able to attenuate spontaneous stereotypic behaviour in deer mice by the selective serotonin reuptake inhibitor (SSRI) fluoxetine next to serotonin 2A/2C and dopamine D2 receptor agonists (Korff et al., 2008), suggesting serotonergic and dopaminergic involvement in the neurobiology of spontaneous stereotypies, thus resembling human OCD. So, by using natural non-pharmacologically induced behavioural disorders, the likelihood of having similar biological underpinnings with human OCD is increased. Further, dogs and humans show an acceptable congruency in brain anatomy and hereditary diseases (Starkey et al., 2005; Cyranoski, 2010). Finally, in previous neuroimaging studies of impulsive aggressive dogs and dogs with an anxiety disorder, we already showed results concerning the regional brain perfusion and serotonergic system (serotonin 2A receptor) as well as treatment outcome with SSRI similar to the ones observed in psychiatric patients (Peremans et al., 2003; Peremans et al., 2005; Vermeire et al., 2009), which strengthens the use of dogs as a model for human psychiatric disorders.

In this study, single photon emission computed tomography (SPECT) was used in combination with the highly selective ^{123}I -fluoropropyl-carbomethoxy-3beta-(4-iodophenyl)tropane (^{123}I -FP-CIT) and ^{123}I -4-amino-N-1-[3-(4-fluorophenoxy)propyl]-4-methyl-4-piperidiny]5-iodo-2-methoxy-benzamide (^{123}I -R91150) to assess respectively the dopamine transporter (DAT) and 5-HT_{2A} receptor availability in 9 drug-naïve compulsive dogs. Based on the recently successful attempt to measure human serotonin transporter (SERT) availability using ^{123}I -FP-CIT (Booij et al., 2007), (hypo)thalamic SERT binding was also calculated. Image fitting was performed on the individual $^{99\text{m}}\text{Tc}$ -ethyl cysteinate dimer ($^{99\text{m}}\text{Tc}$ -ECD) data, also used to assess the regional cerebral blood flow (rCBF). We hypothesised that both neurotransmitter systems would be altered in compulsive dogs compared to healthy dogs. Simultaneously, construct validity as a potential animal model for human OCD was investigated by comparing the results of this study with the OCD neuroimaging literature.

2. Materials and methods

2.1. Subjects

Nine drug-naïve companion dogs (four females and five males; age: 2.55 ± 2.01 years) were used in this study fulfilling the criteria for canine compulsive behaviour (Luescher, 2003). Dogs were recruited from specialised veterinary behavioural medicine practices with

European College of Veterinary Behavioural Medicine–Companion Animals (ECVBM-CA) certified veterinarians. All dogs were diagnosed as having compulsive behaviours, defined as highly patterned, repetitive motor acts (such as tail- and shadow chasing, circling or pattern running) which are exaggerated, time-consuming (more than 1 h a day), performed on a daily basis (for at least 2 months) and significantly interfere with the animal's ethogram. The diagnosis was only definitive after considering all clinical data and history, ruling out other possible causes for the observed behaviour, videotape analysis and agreement concerning the diagnosis between two veterinarians. Disagreement between veterinarians resulted in exclusion of the dog. Validated rating scales, such as the Brown Obsessive–Compulsive Rating Scale (YBOCS), do not yet exist for canine compulsive behaviour. However, only severe cases, exhibiting the compulsive behaviour for at least 3 h a day, were included. Fifteen age-matched healthy, normally behaving dogs (six females and nine males, not significant vs. compulsive dogs (χ^2 -test); age: 2.85 ± 1.83 years, not significant vs. compulsive dogs (Mann Whitney *U* test)) were collected as control group (Tables 1 and 2). No physical, neurological, dermatological or blood work abnormalities were present in both compulsive and control dogs.

Since we previously demonstrated that anxiety (fear, panic) influences the 5-HT_{2A} receptor (Vermeire et al., 2009), we used the validated Canine Behavioural Assessment and Research Questionnaire (CBARQ) (Hsu and Serpell, 2003), to exclude co-morbid behavioural disorders, including aggressive or other anxiety disorders (e.g. separation anxiety, noise phobia), in both groups. Dogs older than 7 years of age were also excluded based on the described age-related decline of DAT and 5-HT_{2A} receptor ligand binding (Peremans et al., 2002a; Salvatore et al., 2003).

In the age-matched healthy control reference group ($n = 15$: 5 Beagles, four Mongrels, two Shepherds, two Terriers, one Weimaraner and one Border Collie) five dogs had both SPECT scans, five had an ^{123}I -FP-CIT and five had an ^{123}I -R91150 acquisition. All had a $^{99\text{m}}\text{Tc}$ -ECD acquisition.

All owners gave written informed consent. The study was approved by the local Ethical Committee (Faculty of Veterinary Medicine, Ghent University).

2.2. Anaesthesia protocol

Anaesthesia was necessary during the different SPECT acquisitions. In brief, sedation was obtained with an intravenous injection of medetomidine hydrochloride (Domitor; Pfizer) $1000 \mu\text{g}/\text{m}^2$ body surface area 30 min before the acquisition. General anaesthesia was induced intravenously with propofol (Propofol; Abbott) and maintained with isoflurane (2% on oxygen; Isoba; Schering–Plough). The duration of the general anaesthesia was limited to the duration of the acquisitions (i.e. 20 to 30 min).

Direct effects by medetomidine or propofol are not described in the literature and unlikely due to the short time interval (10 min) between sedation and acquisition. However, different studies have described isoflurane interference in both serotonergic and dopaminergic system (Votaw et al., 2003; Mukaida et al., 2007). To circumvent this risk, we adhered strictly to the same anaesthetic protocol in all dogs.

2.3. SPECT studies

The SPECT studies were performed using a triple-head γ -camera (Triad, Trionix, Twinsburg, OH, USA) with low energy ultrahigh-resolution parallel hole collimators (tomographic resolution, 8 mm full width at half maximum) positioned as close as possible to the dog's head. Data were acquired for 30 min in step-and-shoot mode (90 steps, 20 s. per step, 4° steps) on a 128×128 matrix. Images were reconstructed with filtered back projection and application of a

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