Understanding deep brain stimulation in obsessive compulsive disorder: A preclinical study into the mechanism of action and behaviour
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Chapter 1

General introduction and thesis outline
1. General introduction

1.1 Obsessive compulsive disorder

Obsessive compulsive disorder (OCD) is a psychiatric disease which is characterized by obsessions resulting in anxiety and by compulsive actions reducing the anxiety. Obsessions are unwanted ideas or impulses that repeatedly well up in the mind, such as persistent fear to harm a loved one, an unreasonable concern with becoming contaminated or an excessive need to do things correctly or perfectly. Compulsions are repetitive behaviours or rituals such as washing and checking, counting, mentally repeating phrases, list making, or endlessly rearranging objects. In the DSM-IV OCD is classified under the category anxiety disorders since anxiety is the core symptom that underlies the disease related behaviour. OCD affects about 2% of the population and begins during childhood and persists throughout a person’s life.

Over the past two decades, it has been suggested that OCD might be related to the brain serotonin system, mainly because of the anti-obsessional efficacy of selective serotonin reuptake inhibitors (SSRIs). The efficacy of SSRIs in OCD compared to the inefficacy of selective noradrenergic and dopaminergic reuptake inhibitors, suggests a specific abnormality of the serotonergic system in OCD (Baumgarten and Grozdanovic1998). However, the exact function of serotonin in OCD is still unclear. Is the serotonergic system implicated in the pathophysiology of OCD, or is it implicated in the treatment effect in OCD? Do SSRIs compensate for a fundamental abnormality of the serotonergic system, or do SSRIs modulate an intact serotonergic system to compensate for another neurotransmitter mechanism such as dopamine?

In line with the last question, several reviews have summarized the growing evidence that dopamine is involved in the pathophysiology of OCD (Denys et al.2004b;Koo et al.2010). For example, atypical antipsychotics with potent 5-HT$_{2A}$, 5-HT$_{2C}$ and D$_2$ antagonistic properties have anti-obsessional properties as additional therapy to SSRIs. Neuroimaging studies have found dopamine transporter binding abnormalities in OCD patients in the basal ganglia (Kim et al.2007;van der Wee et al.2004) and a decreased D$_2$ receptor binding in the ventral striatum (Denys et al.2004a). Moreover, successful SSRI treatment in OCD patients is associated with normalization of an altered dopamine function (Kim et al.2007;Pogarell et al.2005). This shows that besides serotonin, dopamine might also play an important role in OCD.

1.2 Deep Brain Stimulation

First-choice treatment for OCD is SSRIs in combination with cognitive behavioural therapy. If unsuccessful, treatments with clomipramine or combining SSRIs with atypical antipsychotics are the alternatives. Nevertheless, about 10% of OCD patients are therapy-resistant, of
whom half have a severe form of OCD (Denys 2006). For the latter Deep Brain Stimulation (DBS) aimed at the nucleus accumbens (NAc) and ventral striatum/ventral capsule has proven to be an effective treatment for therapy refractory OCD (Denys et al. 2010; Gabriels et al. 2003; Greenberg et al. 2010).

DBS is an adjustable and reversible neurosurgical intervention using implanted electrodes to deliver electrical pulses to areas in the brain. Despite its efficacy in the clinical setting, the mechanism of action of DBS is still uncertain. One of the first hypotheses assumed that DBS causes a functional lesion by suppressing neural activity at the stimulated brain area. This suppression may be achieved by a depolarization blockage, synaptic inhibition or synaptic depression (McIntyre et al. 2004). However, there is also evidence that DBS may activate axons which results in a wide range of effects on local cells and on system levels. These effects involve synaptic inhibition, excitation and prodromic or antidromic activation (Deniau et al. 2010). They may then alter the efflux of neurotransmitters, neuropeptides and retrograde messengers (Tye et al. 2009) or the synchronisation of neural circuits (McCracken and Grace 2009). The latter effect is in line with the hypothesis that DBS results in a modulation of the pathological activity in the neuronal network of the stimulated brain area (McIntyre et al. 2004).

1.3 Outline of the thesis

The overall objective of this thesis was to investigate the effect of DBS in relation to OCD. The PhD project was focused on two complementary directions. First, we examined the mechanism of action of DBS, i.e. the neurobiological underpinnings such as changes in monoamine levels and neurogenesis. Second, we explored the effect of DBS on anxiety and compulsivity, both core symptoms of OCD. To achieve this, DBS was applied in healthy rodents and in an OCD animal model in combination with microdialysis, immunohistochemical techniques and behavioural tests.

In chapter 2 we examined whether the underlying cause of OCD symptoms can be explained by neurobiological alterations of the central serotonergic system. Chapter 2 provides an overview of five lines of evidence that have been cited in support of the serotonin hypothesis: (1) pharmacotherapeutic studies, (2) pharmacotherapy, (3) receptor binding studies, (4) genetic association studies, and (5) animal models.

In chapter 3 to 5, we explored the neurobiological underpinnings of the effect of DBS in the NAc. Drugs that change monoamine levels such as SSRIs or antipsychotic agents are widely used as treatments for OCD. This led us to hypothesize that DBS may have an effect on neuronal release of one or more monoamines. Therefore we initiated studies to determine in vivo monoamine release with microdialysis. In chapter 3 we evaluated the effect of unilateral DBS
in the NAc core on the extracellular concentration of serotonin, dopamine and noradrenaline in the target region. In chapter 4 we extended our microdialysis studies by evaluating the effects of DBS in the NAc core on the extracellular concentration of monoaminergic neurotransmitters in the medial and orbital prefrontal cortex (mPFC and OFC). Recent studies showed that DBS in the NAc core may cause region-specific alterations in local field potential and neuronal responses in the mPFC and the OFC (McCracken and Grace 2007; McCracken and Grace 2009). The mPFC and the OFC are areas of interest given the fact that imaging studies have shown abnormal metabolic activity in both areas in OCD patients which normalized after successful pharmacological treatment (Deckersbach et al. 2006; Evans et al. 2006; Graybiel and Rauch 2000).

A unique aspect of DBS is that it may induce a rapid decrease of some symptoms. However other symptoms, such as compulsions, require a longer stimulation period to improve. This suggests that DBS induces besides acute effects also long term plastic changes in the brain. Therefore we initiated a study into the effect of DBS on neurogenesis. Neurogenesis, the production of new neurons from progenitor cells, is a process that continues throughout adulthood. In an adult matured brain it occurs in two specific regions: the subventricular zone (SVZ) and in the subgranular zone (SGZ) of the hippocampal dentate gyrus (DG). Recent studies showed that DBS in the anterior nucleus of the thalamus, entorhinal cortex and the subthalamic nucleus can increase the cell proliferation in the DG in rodents (Encinas et al. 2011; Khaindrava et al. 2011; Stone et al. 2011; Toda et al. 2008). This led us to hypothesize that DBS in the NAc might modify the cell proliferation in the DG as well. In chapter 5 we investigated this hypothesis by exploring the effect of DBS in the NAc on neurogenesis in the dentate gyrus (DG).

In chapter 6 and 7 we shifted our focus to the effect of DBS on symptoms –anxiety and compulsions- related to OCD. DBS in different targets in the human brain -NAc, BNST, IC and CAU- can induce an immediate decline in symptoms. In particular, anxiety symptoms decrease rapidly after the onset of the stimulation (Denys et al. 2010; Gabriels et al. 2003; Greenberg et al. 2010). It is however unclear which brain area is responsible for this anxiolytic effect. Clinical practice suggests that DBS targeted at the NAc exclusively reduces conditioned anxiety (learned fear) and not the unconditioned anxiety (innate fears). Therefore we hypothesize that stimulation of the NAc uniquely affects conditioned anxiety and not unconditioned anxiety. In chapter 6 we explored this hypothesis by using two specific behavioural paradigms for rodents to examine the effect of DBS in the NAc, BSNT, IC and CAU on conditioned as well as unconditioned anxiety. In chapter 7 we used the sapap3 mutant mouse, an animal model for OCD, to investigate the effect of DBS on compulsive behaviour. Sapap3 is a postsynaptic scaffolding protein at excitatory synapses that is highly expressed in the striatum. Homozygotic mice exhibit compulsive grooming behaviour and increased anxiety. Treatment with SSRIs
reduces these behaviours giving this animal model face and predictive validity. We hypothesize that DBS in the NAc or surrounding areas will alter the compulsive grooming of the sapap3 mutant mice. The effect of DBS in 3 different brain areas - the NAc, BSNT or IC- in the sapap3 mutant mice was investigated to assess its effectiveness to reduce compulsive grooming.

Finally, chapter 8 contains a summary of the main findings presented in this thesis which is followed by a general discussion and suggestions for future research.
Chapter 1

References


