Development of new neurobiological strategies to treat patients with cocaine dependence
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Chapter 1

Introduction and outline
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Introduction

Epidemiology

Cocaine dependence is a chronic relapsing disorder characterized by persistent drug-seeking and drug-taking behaviour, regardless of long-term negative consequences (DSM-IV-TR; American Psychiatric Association, 2000). In this dissertation the term dependence is used interchangeably with the term addiction. Cocaine is the second most commonly used illicit drug after cannabis, and the 2011 World Drug Report states that, in Europe alone, about 4.5-5 million people have used cocaine (UNODC, 2010). Substance dependence (e.g., cocaine dependence) affects people worldwide and creates an immense financial, social and emotional burden on society. Regardless of the motivation to quit and the negative consequences, people with cocaine dependence often relapse and retain an immense feeling of craving towards the drug. An increasing demand for cocaine dependence treatment has been noticed in Europe (EMCDDA, 2011). A similar development has taken place in the Netherlands with currently about 10,000 individuals seeking treatment for cocaine dependence (12% of all patients in addiction treatment), of which about 3,500 have cocaine as their only substance of abuse (Ouwehand et al., 2010).

Neurobiology of addiction

Individual risk factors may influence experimental drug use, drive subsequent use, or maintain compulsive use. Regarding vulnerability for first drug use, environmental factors (including e.g., family conditions, culture, drug availability, and peer pressure) play a key role together with genetic factors. For developing drug dependence, genetic factors (60-80%), peer pressure and life-events (together 20-30%) are believed to constitute the dominant risk factors (Agrawal & Lynskey, 2008; Kendler et al., 2000). This genetic vulnerability is translated into a series of biological risk factors, including low sensitivity for reward (reward deficiency) and deficits in self-control (dissipation).

Low sensitivity for reward (or reward deficiency), mediated by decreased activity of the brain reward circuitry and the neurotransmitters dopamine and glutamate, is an important risk factor for drug use and the development of drug dependence (Comings & Blum, 2000; Volkow et al., 2010). Individuals with decreased sensitivity to rewarding stimuli would be especially driven and motivated to obtain reward (and additionally, take
more risky decisions) (Hommer et al., 2011; Volkow et al., 2004; 2010). Moreover, in individuals at increased risk for drug abuse or dependence, frequent and repeated drug use may lead to a further decrease in the valuation for natural rewards (anhedonia, reward deficiency) (Volkow et al., 2010). In contrast, the presence of inherited increased reward sensitivity (higher availability of postsynaptic dopamine receptors) might be a protective factor against addictive behaviors (Blum et al., 2010; Volkow et al., 1999a; 2006).

Frequent and repeated drug use can lead to increased valuation of drug stimuli relative to natural rewards (increased salience, cue-reactivity) and increased attention to drug-related stimuli (attentional bias), which correlate with alterations of the orbitofrontal cortex, amygdala, and nucleus accumbens mediated by the neurotransmitters dopamine, serotonin and glutamate (Childress et al., 1999; Garavan et al., 2000). Increased attentional bias and cue-reactivity towards drug and associated stimuli have been proposed to represent one of the core mechanisms of drug dependence that lead to compulsive drug seeking, craving and relapse in abstinent drug dependent individuals (Franken et al., 2004). Indeed, increased activity of limbic, prefrontal and anterior cingulate regions have been repeatedly observed in abstinent cocaine-dependent individuals compared to non-drug using individuals during visual drug-related cues (Childress et al., 1999; Garavan et al., 2000; Maas et al., 1998; Wexler et al., 2001). Finally, frequent and repeated drug use can further lead to habit formation and compulsive drug use, which are mediated by dopamine in striatal brain regions and is believed to be associated with a shift from ventral to more dorsal striatal region involvement (Belin & Everitt, 2008).

Impulsivity constitutes another vulnerability factor for drug use, and individuals with poor self-control are more likely to initiate substance use at an early age (Crews & Boettigfer, 2009; Fergusson et al., 2007; Verdejo-Garcia et al., 2008). In many cases, decreased functioning of the inhibitory system and thus poor self-control (dorsolateral prefrontal cortex and anterior cingulated cortex hypoactivation, and serotonin, dopamine, glutamate and gamma aminobutyric acid (GABA) signaling) is observed in drug dependent individuals (Adinoff et al., 2007; de Wit, 2009; Diekhof et al., 2011; Pavlov et al., 2011). During response inhibition tasks, cocaine dependent individuals generally showed lower activation of the dorsolateral prefrontal cortex and anterior cingulated cortex compared to non-drug using individuals (Hester & Garavan, 2004; Kauffman et al., 2003; Li et al., 2008; Meade et al., 2011; Crunelle et al., submitted).

Thus, in many processes related to the development or persistence of drug dependence, including reward sensitivity, impulsivity, salience/craving, and compulsive drug seeking, dopamine is one of the neurotransmitters that play an important role. This dissertation focuses mainly on dopamine and its role in reward deficiency, a hypothesis
that states that inadequate functioning of the reward system (where natural rewards fail to activate the dopaminergic reward circuitry adequately and drug use is experienced as especially rewarding) leads to the repeated and persistent drug use despite negative consequences (Gould et al., 2011; Hommer et al., 2011). In addition, this thesis looks at the role of dopamine transporters (DATs) in the treatment of attention deficit/hyperactivity disorder (ADHD) patients with a comorbid diagnosis of cocaine dependence.

**Cocaine dependence**

Cocaine intake results in an acute increase of extracellular dopamine in the brain due to binding of cocaine to the DAT. The blockage of dopamine reuptake from the synaptic cleft and the fast pharmacokinetic characteristics of cocaine are associated with its reinforcing effects (Kuhar et al., 1991; Ritz et al., 1987). Frequent and repeated stimulation of the dopaminergic system activates and alters the reward circuitry in the brain, including frontal and striatal brain areas (Volkow et al., 1996). Additionally, following repeated use, dopamine release also occurs when drug use is expected (Schultz et al., 2000), contributing to the immense feeling of craving towards cocaine upon repeated use. Finally, it is hypothesized that frequent and chronic drug use renders the dopaminergic reward system hypoactive (Nader et al., 2006; Nikolaus et al., 2007; Volkow et al., 2007). One of the most consistent findings in cocaine dependence is a decreased availability of postsynaptic striatal dopamine D₂ receptors after repeated drug use probably due to receptor down regulation following high synaptic dopamine concentrations (Martinez et al., 2004; 2009; Thanos et al., 2008; Volkow et al., 1990; 1993). However, some individual recovery in dopamine D₂ receptor availability was observed following abstinence both in rodents and in humans (Nader et al., 2006; Volkow et al., 1990). Also, some evidence suggests that the dopamine D₂ receptors might be implicated in the perception of the ‘high’ associated with cocaine use, and indicates that low levels of dopamine D₂ receptors might also be required for drugs to be distinguished as specifically reinforcing (Volkow et al., 1999b). It should be noted here that there is still discussion on whether decreased dopamine D₂ receptor availability is the cause or the consequence of drug use or both (Agrawal & Lynskey, 2008; Volkow et al., 1999a).

**Treatment of cocaine dependence**

Several pharmacological compounds targeting different neurotransmitter systems have been tested to reduce craving and prevent relapse in cocaine dependent patients (e.g., topiramate, vigabatrin, citalopram, aripiprazole, cabergoline, methamphetamine, dex-
ampheta mine, modafinil, disulfiram; van den Brink et al., 2011), but have thus far neither been very successful nor very popular, and these medications are often associated with important side effects or involve the administration of stimulant-like medications (e.g., the amphetamines), which may create a dopamine-mediated abuse liability. Thus far, no compound has been registered for the indication cocaine dependence (van den Brink et al., 2011). It has been proposed, however, that upregulation of the dopamine D₂ receptors may result in potentially effective pharmacotherapy for substance use disorders, including cocaine dependence and other reward deficiency disorders (Blum et al., 2008a; Nader et al., 2006; Thanos et al., 2005; 2008). In this regard, it is of interest that, in rats, increasing dopamine D₂ receptor availability (by DNA transfer using an adenovirus) in the nucleus accumbens resulted in a significant reduction in cocaine self-administration (Thanos et al., 2008).

**Varenicline as a new treatment option for cocaine dependence**

In this regard, pharmacotherapy with varenicline, an α4β2 nicotinic acetylcholine receptor partial agonist, may be of interest. Varenicline is effective for smoking cessation due to its agonist-antagonist profile and probably partly by its indirect effects on the dopaminergic system. Firstly, varenicline functions as an agonist on the nicotinic acetylcholine receptors with a relatively low intrinsic activity, thereby maintaining low to moderate levels of extracellular dopamine release to decrease withdrawal symptoms after smoking cessation. However, when smoking, varenicline mainly functions as an antagonist of nicotine at the nicotinic acetylcholine receptors, thereby reducing smoking satisfaction (Cahill et al., 2011; Coe et al., 2005a). Activation of the α4β2 nicotinic acetylcholine receptors activates dopamine release (Rollema et al., 2007), and thus partial blocking of the nicotinic receptor could result in upregulation of postsynaptic dopamine receptors by decreasing dopamine release. Consequently, although speculatively, a hypothesis would be that its efficacy in smoking cessation and the prevention of relapse might be related to an increase of striatal dopamine D₂ receptor levels.

Varenicline reduces alcohol seeking in rats (Bito-Onon et al., 2011; Steensland et al., 2007; Wouda et al., 2011) and decreases craving in heavy alcohol dependent individuals (Fucito et al., 2011). Additionally, one recent clinical trial in cocaine dependent patients showed that varenicline treatment decreased cocaine use and craving compared to placebo (Plebani et al., 2011). Subsequently, one may propose that varenicline or other nicotinic partial agonists might be an effective pharmacotherapy for cocaine dependence, possibly by increasing dopamine D₂ receptor availability.
Cannabinoid receptor antagonists as a new treatment option for cocaine dependence

Animal studies have shown an increase in relapse rates following stimulation of the cannabinoid system (de Vries et al., 2001), thereby proposing a role for cannabinoid antagonists as potential compounds to reduce relapsing episodes in cocaine dependence (De Vries and Schoffelmeer, 2005; Le Foll & Goldberg, 2005). Several preclinical studies have been conducted with the cannabinoid CB1 receptor antagonist rimonabant on cocaine, nicotine, and alcohol seeking and showed reduced drug self-administration and reduced motivation for drug intake (Le Foll & Goldberg, 2005; Ward et al., 2009; Yu et al., 2011). However, while clinical trials have shown that rimonabant has moderate efficacy for smoking cessation (Cahill & Ussher, 2011), another cannabinoid receptor antagonist (surinabant) has not (Tonstad & Aubin, 2012), and it is unclear whether cannabinoid receptor antagonists are also effective for alcohol dependence (Soyka et al., 2008; George et al., 2010). The cannabinoid system is in close interaction with the dopaminergic system, and subsequently rimonabant might (indirectly) exert its effect through dopamine D2 receptor availability, thereby reducing drug intake and craving. More specifically, stimulation of cannabinoid receptors leads to dopamine release, and blocking the cannabinoid CB1 receptor might, therefore, reduce dopamine release resulting in increased dopamine D2 receptor availability postsynaptically.

Treatment of comorbid ADHD in cocaine dependent patients

Psychiatric disorders, including ADHD, often co-occur with cocaine dependence and negatively influence treatment outcome in cocaine dependence (Delavenne et al., 2011; Fayyad et al., 2007; Kelly et al., 2012; Kessler et al., 1996; Levin et al., 2007). ADHD is an important risk factor contributing to cocaine dependence, which can be explained largely by the commonalities between both disorders, including genetic predispositions, impulsivity, and altered reward sensitivity in ADHD patients (e.g., Bukstein, 2011; Wilens and Morrison, 2011). Indeed, impulsivity is a key characteristic of ADHD pathology, and ADHD is hypothesized to constitute a subtype of reward deficiency syndromes (Blum et al., 2008b). In general, ADHD can be treated successfully by methylphenidate, a compound that, like cocaine, also binds to the DAT, where it blocks the reuptake of dopamine from the synaptic cleft. Methylphenidate is, however, less effective in ADHD patients with cocaine-dependence than in ADHD patients without a substance use disorder (Levin et al., 1998; 2007; Schubiner et al., 2002; Szobot et al., 2008), but the underlying reason for this lack of efficacy remains unclear. Differences between ADHD patients with and
without cocaine dependence in the availability and occupancy by methylphenidate of DATs could be a possible explanation for the low success rates in ADHD patients with a comorbid substance use disorder.

**Visualization of dopamine receptors and transporters in-vivo**

Nuclear imaging techniques such as positron emission tomography (PET) or single photon emission computed tomography (SPECT), using radiopharmaceuticals that bind to the specific receptor of interest, are widely used in clinical settings and allow the measurement of receptor availability and receptor occupancy after pharmacotherapy. In this regard, the radiopharmaceuticals \[^{123}I\]IBZM (iodobenzamide) and \[^{123}I\]FP-CIT (N-\(\omega\)-fluoropropyl-2\(\beta\)-carbomethoxy-3\(\beta\)-\{4-iodophenyl\}nortropane) are well-validated radioligands to assess in-vivo dopamine D\(_2\)-like receptors and DATs, respectively, and have been used frequently in preclinical and clinical studies (Booij et al., 1997; Verhoeff et al., 1991).
Outline of this dissertation

The second part of this dissertation starts with a review on the potential usefulness of a partial agonist for nicotinic acetylcholine receptors to treat cocaine dependence (Part 2: Chapter 2). Subsequently, this dissertation describes a series of preclinical studies on the nicotinic partial agonist varenicline (Champix®) (Part 2: Chapters 3-5) and a preclinical study on the effects of the cannabinoid antagonist rimonabant (Accomplia®) (Part 2: Chapter 6) using storage phosphor and SPECT imaging. Using the radiotracer $^{123}$IIBZM, the hypothesis was tested that chronic treatment with varenicline and rimonabant may increase dopamine D$_2$ receptor availability.

The third part of this dissertation starts with a meta-analysis on the prevalence of ADHD in treatment seeking substance use disorder patients (Part 3: Chapter 7) and is followed by a clinical trial comparing ADHD patients with and without a comorbid diagnosis of cocaine dependence and to better understand the lack of effect of methylphenidate treatment in the comorbid group (Part 3: Chapter 8). More specifically, using $^{123}$FP-CIT as a radiotracer, we measured DAT availability and DAT occupancy by methylphenidate in ADHD patients with and without comorbid cocaine dependence, to test the hypothesis that increased DAT availability and decreased DAT binding by methylphenidate is responsible for the lack of effectiveness in ADHD patients with comorbid cocaine-dependence.

This dissertation ends with a summary, discussion, and concluding remarks (Part 4: Chapter 9).