Development of new neurobiological strategies to treat patients with cocaine dependence

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Chapter 9:

Summary, discussion and conclusions

Summary

Dopamine is a key neurotransmitter in the pathophysiology of substance dependence and low striatal dopamine D_2 receptor availability is probably both a risk factor for and a consequence of repeated drug use. It was, therefore, hypothesized that increasing dopamine D_2 receptor avalaibility is a promising strategy to treat drug dependence (Part 1: Chapter 1). Varenicline (an $\alpha 4\beta 2$ nicotinic partial agonist registered for smoking cessation) and rimonabant (a cannabinoid CB_1 receptor antagonist previously registered for obesity treatment) seem good candidates for further investigation as potential treatments of cocaine dependence, because our studies showed that both compounds increase dopamine $D_{2/3}$ receptor availability in striatal brain regions of drug-naïve rats as measured by storage phosphor and SPECT imaging (Part 2: Chapters 2-6).

Approximately one out of every four patients with a substance use disorder has a comorbid attention-deficit/hyperactivity disorder (ADHD) (Part 3: Chapter 7). This comorbidity significantly worsens treatment outcome and has a negative influence on the pharmacotherapeutic effectiveness of methylphenidate in the treatment of ADHD. Our study showed that this may be attributed to lower availability of striatal dopamine transporters (DATs) and decreased DAT occupancy by methylphenidate in ADHD patients with cocaine dependence compared to ADHD patients without cocaine dependence (Part 3: Chapter 8). However, ADHD treatment response was not associated with DAT availability at baseline or DAT occupancy by methylphenidate, suggesting that higher doses of methylphenidate are not very likely to result in better outcomes and that other types of medication should be tested in ADHD patients with cocaine dependence such as the selective noradrenaline re-uptake inhibitor atomoxetine or the dopamine and noradrenaline releaser (lis)dexamphetamine.

Discussion, Clinical Relevance and Future Studies

In the next paragraphs, we discusss our findings and their clinical relevance and describe some proposals for future studies.

Varenicline increases dopamine D_2 receptor availability in drug-naïve rats

Discussion

In our first experiments (Part 2: Chapters 3-5), we assessed the effects on striatal dopamine $D_{2/3}$ receptor availability following chronic administration of the nicotinic partial agonist varenicline. These experiments compared the effects of chronic varenicline treatment directly with chronic saline administration in two groups of rats (varenicline- and saline-treated groups). In these experiments, we found an increase of dopamine $D_{2/3}$ receptor levels in varenicline treated rats.

Varenicline is a partial agonist and its effect in the brain is dependent on the baseline level of nicotinic receptor occupation. Because we imaged drug-naïve rats, with no previous additional nicotinic/acetylcholinergic stimulation, varenicline may have acted as an agonist on the nicotinic acetylcholine receptors, thereby possibly enhancing synaptic dopamine levels. An elevation of dopamine levels would logically result in a decrease of postsynaptic dopamine D_2 receptor availability (due to down-regulation following the continuous presence of extracellular dopamine), but, instead, we found increased availability of dopamine D_2 receptors after varenicline treatment. There are several post hoc explanations for the fact that chronic treatment of varenicline increased dopamine D_2 receptor availability in drug-naïve rats. Firstly, *acute* varenicline administration in drug-naïve rats enhances striatal extracellular dopamine levels (Rollema et al., 2007), but the effects of *chronic* varenicline administration have not yet been investigated. Hypothetically, varenicline may have a blunted effect on dopamine release during chronic administration, subsequently resulting in increased dopamine D_2 receptor availability. To test this hypothesis, it is important to evaluate the effects of chronic varencline treatment on dopamine release (e.g., using microdialysis). Secondly, chronic varenicline administration may modulate dopamine signaling through glutamate and GABA interneurons, as nicotinic receptors are present on glutamate and GABA neurons in dopamine-rich brain areas including the striatum (Jones & Wonnacott, 2004). Varenicline might stimulate GABAergic neurons and/or block glutamatergic neurons, two effects that have shown to decrease nicotine self-administration in rats (Markou et al., 2004). Finally, varenicline may have (direct) effects on genes or regulatory proteins associated with the expression of dopamine

D_2 receptors (e.g., Ito et al., 1999; Kim et al., 2001). This may lead to dopamine D_2 receptor upregulation that is not primarely dependent on dopamine signaling.

It should be noted here that varenicline was also shown to be effective in reducing alcohol-seeking and alcohol intake in rats (Chatterjee et al., 2011; Steensland et al., 2007). By elucidating the mechanism of action for increased dopamine D_2 receptors following chronic varenicline administration in drug-naïve rats, one may also find a possible explanation for the efficacy of varenicline in alcohol dependence and in reducing alcohol-seeking or other drugs of abuse in rats.

Clinical relevance

The clinical relevance of the presented studies on varenicline in small laboratory animals is not straightforward and clinical studies on the effects of varenicline on dopamine D_2 receptor availability have not been performed yet. If one wants to extrapolate these findings to the human situation, several questions arise. For example, since cocaine dependent patients are commonly also smokers, varenicline might work as an antagonist and consequently our results in non-smoking drug-naive rats may not be generalisable to smoking cocaine abusers.

Also, in individuals with cocaine dependence, altered functionality of the prefrontal cortex, anterior cingulated cortex, and amygdala have been observed related to craving (Childress et al., 1999; Garavan et al., 2000; Maas et al., 1998; Wexler et al., 2001; Crunelle et al. submitted). However, the effects of varenicline on dopamine receptor availability in other brain regions associated with craving, including the frontal cortex, cingulated cortex, and amygdala, have not been assessed in the present animal studies, partly because of the properties of the used radiotracer. [^{123}I]IBZM binds to both dopamine D_2 and D_3 receptors with affinities in the low nanomolar range (Videbaek et al., 2000). Therefore, this tracer can be used to assess receptor binding adequately in brain areas that express these receptors extensively (i.e., basal ganglia). However, in extrastriatal brain regions, dopamine D_2 receptors are present at a much lower density and can only be measured in-vivo accurately using $D_{2/3}$ radiotracers with a very high affinity for these receptors (picomolar range) such as the PET ligand [^{18}F]fallypride, the SPECT ligand [^{123}I]epidepride and the PET ligand [^{11}C]FLB 457 (Janowsky et al., 1992; Kegeles et al., 2008; Olsson et al., 2004). Increasing dopamine D_2 receptor availability in extrastriatal brain regions may have an effect on how drug-related stimuli are processed in drug-dependent individuals. Speculatively, in humans, varenicline may have a specific effect on the prefrontal cortex, and this might directly relate to impulsivity rather than craving, making varenicline possibly effective on reducing drug consumption through decreasing impulsive behavior.

Although the $\alpha4\beta2$ receptor subtype is predominantly present on dopaminergic cell bodies in striatal brain regions (Clark & Pert, 1985; Zhou et al., 2003), recent imaging studies support the concept that striatal dopamine function can not be regarded as an index of global dopamine brain function, since D_2 receptor availability in striatum and extrastriatal brain areas may not be correlated (Cervenka et al., 2010). This further highlights the need to study the effects of varenicline on extrastriatal D_2 receptors.

Molecular imaging studies in cocaine dependent individuals showed 11-15% lower striatal dopamine D_2 receptor availability compared to healthy controls (Martinez et al., 2004; Volkow et al., 1997). In drug-naïve rats, varenicline treatment resulted in 13-14% (Crunelle et al., 2009; 2011) and 48% (Crunelle et al., 2012) increases in striatal dopamine D_2 receptor availability (Part 2: Chapters 3-5). Interestingly, the observed increases on striatal dopamine $D_{2/3}$ receptor availability following varenicline treatment are in the same range as the range of decrease in dopamine D_2 receptor availability reported in human cocaine dependent patients. Therefore, a small increase in dopamine D_2 transporter availability of 10-15% might be enough to normalize the decreased dopamine D_2 receptor availability found in drug addiction, but this should be investigated further in clinical trials.

The findings of sustained dopamine $D_{2/3}$ receptor availability upon treatment discontinuation might be another important attribute of varenicline in the treatment of cocaine dependence, since cocaine dependent patients tend to have a relatively low adherence for medication intake related to substance abuse (Velligan et al, 2010). Low adherence rates in substance use dependent patients may be related to the relatively longer time period necessary to induce treatment effect, whereas drug intake provides an immediate effect. Moreover, the possible confounding effects of medication use (adverse effects when combining medication use with drug use; or decreased effect of drug 'high' during treatment) would add to the low treatment compliance in drug abusing populations. The fact that varenicline induces an increase of dopamine $D_{2/3}$ receptor availability following two week treatment, and that the effect of varenicline lasted for at least two weeks after treatment discontinuation, provides another argument for the use of varenicline in the treatment of cocaine dependence. This is also consistent with findings from clinical studies on the effect of varenicline in nicotine-dependent populations, where it was shown that significantly more participants remained abstinent from smoking 28 weeks following (24 week) treatment discontinuation than when patients where randomized to placebo (Aubin et al., 2008). Of course, these interpretations are purely speculative because the studies presented in this dissertation were all performed in rats, and we have no evidence for an effect on dopamine release in our studies.

Future studies

Previous studies have shown that varenicline can reduce alcohol use in rodents (Chatterjee et al., 2011; Steensland et al., 2007). However, no data are available on the effect of varenicline on dopamine D_2 receptor availability and drug use in rodents. Therefore, future animal studies should investigate the potential of chronic varenicline administration to reduce drug self-administration (cocaine or other drugs of abuse) to see whether reductions in self-administration are related to the increase of dopamine D_2 receptor availability. Regarding the mode of action of varenicline (agonistic versus antagonistic), it would be of interest not only to study drug-naïve rats but also nicotine-pretreated rats. Additionally, to better understand the underlying pharmacological mechanism leading to increased dopamine D_2 receptor availability, one may investigate how varenicline increases dopamine D_2 receptor availability in drug-naïve rats, e.g., by a (relative) reduction of dopamine release, which can be assessed with in-vivo microdialysis. Although initial experiments showed a significant increase in dopamine release following acute varenicline administration in rats (Rollema et al., 2007), it is not known whether this is also the case after chronic administration.

Additionally, one should further investigate the effects of varenicline on prefrontal and amygdalar brain regions, more specifically by investigating the effects on dopamine release (using e.g., in-vivo microdialysis; Rollema et al., 2009; 2011) and on extrastriatal dopamine D_2 receptor availability (using e.g., [^{18}F]fallypride PET, [^{11}C]FLB 457 PET, or [^{123}I]epidepride SPECT).

If we can show an increase of dopamine D_2 receptors in the proposed studies in drug-habituated animals, this may support the start of human trials. More specifically, randomized clinical trials may assess the efficacy of varenicline in reducing relapse and cue-induced craving in cocaine dependent patients, while imaging the effects of varenicline on cue-induced reactivity (fMRI) and on striatal dopamine D_2 receptor availability in cocaine dependent patients (SPECT or PET). Thus far, two studies reported that the use of varenicline was safe in cocaine dependent patients (Plebani et al., 2011; Poling et al., 2010). One study reported lower odds of cocaine use (Plebani et al., 2011), while the other failed to find difference in cocaine use between varenicline and placebo (Poling et al., 2010). These discrepant findings may be due to the small number ($N = 31$: 18 in the placebogroup and 13 in the varenicline group) of very complex patients (cocaine patients maintained on methadone) in the Poling et al. (2010) study. Moreover, the study design was very complex with the initiation of methadone treatment and the treatment with varenicline spearated only by one week. Finally, Poling and colleagues (2010) did not assess cocaine *craving* per se, and the study was primarely aimed at reducing nicotine use.

In contrast, the study by Plebani et al. (2011) was conducted in a homogeneous sample of 37 cocaine dependent patients (without heroine dependence comorbidity) and was solely directed at the reduction of cocaine use by varenicline administration in combination with contingency management in order to enhance treatment ccompliance. In this study, varenicline treated patients had fewer cocaine positive urines and reported lower levels of subjective cocaine reward. Varenicline might, therefore, mainly reduce cocaine reward and cocaine use in cocaine dependent patients without polydrug use and simultaneously treated with contingency management to improve compliance. Additionally, imaging of striatal dopamine D_2 receptor availability following varenicline treatment could also be performed in smokers and non-smokers to assess whether increasing dopamine D_2 receptor availability is directly related to the efficacy of varenicline in smoking cessation. Finally, using radiotracers that bind with high affinity to $\alpha4\beta2$ nicotine acetylcholine receptors (e.g., [^{123}I]-5-IA-85380, Staley et al., 2005), one could image whether the occupancy of nicotinic receptors by varenicline is related to treatment efficacy or reduction in craving in cocaine dependent and/or nicotine dependent individuals.

Rimonabant increases dopamine D_2 receptor availability in drug-naïve rats

Discussion

Rimonabant, like varenicline, also increased dopamine $D_{2/3}$ receptor availability (Part 2: Chapter 6). The most direct explanation for an increase in striatal dopamine D_2 receptor availability is an upregulation of these receptors postsynaptically as an adaptation mechanism following reduced synaptic dopamine release. Reduced dopamine release could occur following blockage of cannabinoid signaling (using a cannabinoid receptor blocker, e.g., rimonabant), e.g., due to direct blockage of cannabinoid signaling on dopamine terminals. Reducing cannabinoid signaling would subsequently reduce dopamine signaling, which would result in increased dopamine D_2 receptor levels post-synaptically. Alternatively, other mechanisms might be involved, including glutamate and GABA signaling. Cannabinoid receptors located on inhibitory and excitatory nerve terminals targetting dopamine neurons modulate dopamine release (Lupica & Riegel, 2005; Van der Stelt & Di Marzo, 2003). Therefore, cannabinoid CB_1 blockage could also result in altered glutamate and GABA signaling and a subsequent reduction of dopamine release (decreasing synaptic dopamine levels) and increasing dopamine D_2 receptor availability. Finally, cannabinoid CB_1 receptor antagonists might also have an effect on regulatory proteins or transcription genes that (directly) upregulate dopamine receptor availability, e.g., by

decreasing kinase proteins (leading to increased sequestration of D_2 receptors; Ito et al., 1999), by decreasing dynamin availability (leading to reduced internatization of D_2 receptors; Kim et al., 2001), or by altering kinases activity (leading to receptor phosphorylation and subsequent activation or deactivation of proteins; Kim et al., 2001), but the effects of cannabinoids here have not previously been investigated. These latter options could represent a common mechanism of action with varenicline to increase dopamine D_2 receptor availability, regardless of altered dopamine signaling.

Clinical relevance

Rimonabant was (until recently) registered for the treatment of obesity, a condition that has been associated with decreased dopamine D_2 receptor availability in humans (Fehr et al., 2008; Wang et al., 2001; de Weijer et al., 2012). Additionally, obesity involves brain circuitries that overlap with other reward deficiency disorders, characterized by decreased D_2 receptor availability, like substance dependence (Volkow et al., 2011). Furthermore, there is evidence that rimonabant is also effective for smoking cessation (Cahill & Ussher, 2011), although the cannabinoid receptor antagonist surinabant is probably not effective for smoking cessation (Tonstad & Aubin, 2012), but it is not clear if this is also the case for alcohol dependence (Soyka et al., 2008; George et al., 2010). Therefore, one might hypothesize that the efficacy of rimonabant in reducing food and/or drug intake and the decreasing reward associated with food and/or drug are associated with increases in striatal dopamine D_2 receptor availability. Our study (Part 2: Chapter 6) support this hypothesis by providing evidence that, in drug-naïve rats, one can increase striatal dopamine D_2 receptor availability by chronic administration of rimonabant.

Future studies

Rimonabant was taken off the market due to post-marketing reports of adverse events, including depressed mood and suicidality. Subsequently, clinical trials should be performed using cannabinoid antagonists other than rimonabant in obese or drug-dependent patients, to assess whether an increase in dopamine D_2 receptor availability is related with reduced food or drug intake or reduced subjective reward effects for these stimuli. Of course, these studies will have to pay serious attention to the possible occurence of mood problems and suicidal ideation. Thus far, no other cannabinoid CB_1 receptor antagonists have been licensed for clinical use. Our study, however, provides support for the further investigation of cannabinoid receptor antagonists as possible effective treatments for reward-like disorders, such as obesity and drug addiction.

Additionally, using new specific radiotracers, it is now feasible to measure cannabinoid CB_1 receptor availability *in-vivo* in humans (Burns et al., 2007), and it would be interesting to measure cannabinoid receptor occupancy following rimonabant treatment, and assess whether baseline receptor availability or occupancy by pharmacological treatment is related to treatment response. Indeed, a recent study showed that CB_1 availiblity is related to novelty-seeking, a risk factor for developing addictive behaviours (van Laere et al., 2009).

Lower treatment efficacy by methylphenidate in ADHD and cocaine dependence

Discussion

In part 3, we provide evidence of lower baseline striatal dopamine transporter (DAT) availability and lower DAT occupancy by methylphenidate in cocaine dependent patients with comorbid ADHD compared to ADHD patients without comorbid cocaine dependency. However, there were no correlations between baseline DAT or DAT occupancy by methylphenidate and ADHD symptom improvement. These results suggest that other differences than DAT occupancy by methylphenidate might be responsible for the reduced effectiveness of methylphenidate in patients with ADHD and comorbid cocaine dependence. It should be noted, however, that this dissertation primarily focused on the dopaminergic system and that other neurotransmitter systems are also important in drug dependence, including serotonin, noradrenaline and glutamate (e.g., Cox et al., 2011; Nonkes et al., 2011; Schmaal et al., 2011). For example, glutamate transmission is associated with relapse in cocaine addiction (Cornish & Kalivas, 2000), and N-acetylcysteine was found to reduce cocaine-seeking in rats (Zhou and Kalivas, 2008) and reduced subjective reward following nicotine smoking (Schmaal et al., 2011). Many other neurotransmitter systems are also currently investigated for their potential in the treatment of cocaine dependence (Shorter & Kosten, 2011; van den Brink et al., 2011). Subsequently, it is possible that availability and/or occupancy of other neurotransmitter systems might be more indicative for the decreased treatment response in ADHD patients with comorbid cocaine dependence, e.g., the noradrenaline transporter system and occupancy of noradrenaline transporters by methylphenidate. Indeed, methylphenidate also binds to noradrenaline transporters (Hannestad et al., 2010). However, we did not investigate noradrenaline transporter availability and/or occupancy by methylphenidate in ADHD patients with and without cocaine dependence.

Clinical relevance

Abstinent cocaine dependent patients with comorbid ADHD might benefit from medications directed at non-dopaminergic pharmacological targets, such as the selective noradrenaline reuptake inhibitor atomoxetine. Atomoxetine alleviates symptoms of ADHD, and increases noradrenaline and dopamine levels in prefrontal cortex, without elevating extracellular dopamine levels in striatal brain regions or in the nucleus accumbens (Bymaster et al., 2002). Increasing signaling in the frontal cortex would reduce impulsivity levels (beneficial in both ADHD and cocaine dependence), without increasing dopamine activation in limbic brain regions (related to craving, and abuse potential). In cocaine dependence, atomoxetine reduced cue-illicit cocaine seeking and enhanced the long-term extinction of cocaine seeking in rats, resulting in a reduction of relapse (Janak et al., 2011; Economidou et al., 2011), and in a 12-week open trial in cocaine abusing ADHD patients, atomoxetine reduced ADHD symptoms in cocaine dependent patients (3 out of every 4 patients had over 30% improvement in ADHD symptom reduction), but it did not reduce cocaine use (Levin et al., 2009).

Another possibility in the treatment of ADHD patients with cocaine dependence is dexamphetamine (and its prodrug lisdexamphetamine), a dopamine and noradrenaline releaser used for the treatment of ADHD. Dexamphetamine is often prescribed in ADHD patients that do not respond to methylphenidate treatment, and might therefore be another possibility for the treatment of ADHD patients with comorbid cocaine dependence. In chapter 1, we have pointed at possible abuse liability when using stimulants in the treatment of subpopulations of drug dependent individuals. However, lisdexamphetamine is more difficult to abuse due to the need for conversion of the prodrug to the active drug. Only following oral administration, the l-lysine unit is cleaved from the parent compound via enzymatic biotransformation in the intestines and liver. In cocaine-dependent patients and in animal studies, chronic treatment with dexamphetamine reduced cocaine use and cocaine reinforcement (Czoty et al., 2010; Grabowski et al., 2001; Negus & Mello 2003; Shearer et al., 2003), and also showed effectiveness of long-acting stimulants (including methylphenidate and dextroamphetamine) in ADHD patients with comorbid cocaine dependence (Castaneda et al., 1999).

In summary, treatment strategies oriented at combined dopaminergic and noradrenergic stimulation (lisdexamphetamine and atomoxetine) might be more effective for the treatment of ADHD in cocaine dependent patients than (high doses of) methylphenidate.

Future studies

In cocaine dependent patients with comorbid ADHD, we propose randomized clinical trials that assess the efficacy of medications as atomoxetine and dexamphetamine, in the specific subpopulation of cocaine-dependent ADHD patients. Future studies might also look at the possible reduced binding of methylphenidate to noradrenaline transporters (Hannestad et al., 2010), to assess whether treatments oriented mainly at noradrenaline transporter blockage might be more effective in ADHD populations with comorbid cocaine dependence.

Additionally, a recommendation for future studies is the combination of molecular imaging techniques like SPECT or PET and magnetic resonance imaging (MRI) techniques, which would provide simultaneous structural, functional, and biochemical information on the neurobiological bases of the treatment response in cocaine dependent individuals.

Finally, it should be noted that this dissertation does not provide a full overview of neurobiological strategies to treat cocaine dependence and that it would be of interest if future studies would also focus on the role of other neurotransmitter systems in relapse prevention. More specifically, several treatments aimed at e.g., serotonin, noradrenaline, GABA or glutamate systems have been investigated in cocaine dependence (van den Brink et al., 2011), but it is not yet clear whether the efficacy of serotonin, noradrenaline, GABA or glutamate treatments are directly related to their interaction with the dopaminergic system (e.g., Nutt, 2011). Perhaps, alterations of the serotonin, noradrenaline, GABA or glutamate systems can also reduce relapse without a main effect on dopaminergic signaling and this should be investigated more closely in future studies.