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CHAPTER 1

INTRODUCTION
The neurotransmitter dopamine is involved in various physiological central nervous system (CNS) functions as well as the pathogenesis of several neuropsychiatric disorders, including Parkinson’s disease, schizophrenia, drug addiction and hyperprolactinemia. Pharmacological methods to alter dopamine neurotransmission currently have only limited efficacy in alleviating the symptoms of these disorders, but adverse side effects can be debilitating. Thus, improvement of dopaminergic pharmacotherapy remains a high priority. This thesis describes several early phase drug development trials with novel compounds that aim to improve dopaminergic pharmacotherapy by various strategies. This introductory chapter provides an overview of dopamine neurotransmission and the various disorders associated with dopaminergic systems. Also, several pharmacological strategies for improvement of dopaminergic pharmacotherapy as well as the specific aims of the following chapters of this thesis are outlined.

**DOPAMINE NEUROTRANSMISSION**

Dopamine is a monoamine neurotransmitter, which is produced by neurons in the midbrain and hypothalamus. The synthesis of dopamine starts with the uptake of tyrosine from blood by amino acid transporters. Once inside the neuron, tyrosine is converted to L-dopa by the cytosolic enzyme tyrosine hydroxylase (TH), which is the rate-limiting enzyme in dopamine synthesis. In turn, L-dopa is converted to dopamine by the cytosolic enzyme aromatic L-amino acid decarboxylase (AAAD). Subsequently, dopamine is transported from the cytoplasm into storage vesicles. Upon arrival of an action potential, the storage vesicles discharge their dopamine contents into the synaptic cleft by means of exocytosis. Dopamine traverses the synaptic cleft and binds to receptors on the postsynaptic neuron. Five different types of dopamine receptors have been characterized, termed the D₁, D₂, D₃, D₄ and D₅ receptor, all of which are G protein-coupled receptors. D₁-like receptors (which include the D₁ and D₅ receptor subtypes) are stimulatory Gₛ-coupled receptors and D₂-like receptors (which include D₂, D₃ and D₄ receptor subtypes) are inhibitory Gₛ-coupled receptors. Two major isoforms of the D₂ receptor exist due to alternative splicing, termed D₂-short (or D₂S) and D₂-long (or D₂L) receptors. The D₂L receptor appears to be expressed mostly on postsynaptic membranes, while the D₂S receptor appears to be expressed mostly on presynaptic membranes and to be involved in auto-receptor function. Neurotransmitter action is terminated by the reuptake of dopamine by dopamine transporters (DAT) that actively pump extracellular dopamine from the synapse back into the nerve terminal.
The perikarya of most dopaminergic neurons are located in the substantia nigra and ventral tegmental area of the mesencephalon and in the periventricular and arcuate nuclei of the hypothalamus. The dopaminergic neurons project to various brain structures through several anatomically organized pathways (see Table 1 and Figure 1), including:

- The nigrostriatal pathway originates in the substantia nigra and projects to the striatum and acts to modulate the output activity of the striatum. This pathway is involved in various motor and cognitive functions.
- The mesocortical pathway originates in the ventral tegmental area and projects to the prefrontal, insular, motor and sensory cortices. This pathway is involved in encoding and use of working memory information by prefrontal cortex circuits.
- The mesolimbic pathway originates in the ventral tegmental area and projects to the limbic cortices, hippocampus, nucleus accumbens and amygdala. This pathway is involved in reward and reinforcement mechanisms and appears to encode prediction of reward and facilitate learning of reward associations.
- The tuberoinfundibular pathway originates in the periventricular and arcuate nuclei of the hypothalamus and projects to the external zone of the median eminence, and is involved in hypothalamic inhibitory control of prolactin secretion.
- Dopaminergic neurons in the area postrema and nucleus tractus solitarius are involved in the control of emesis.

Dopamine neurotransmission is under stimulatory and inhibitory control of various other neurotransmitters. Furthermore, the presence of various feedback mechanisms, modulatory influence of interneurons and interactions between neurotransmitters ultimately result in very complex neurocircuits. In general, dopamine neurotransmission is stimulated by glutamate and inhibited by γ-aminobutyric acid (GABA) (see Figure 2), with further modulatory roles of serotonin, acetylcholine, tachykinin neuropeptides, as well as several others.

**DISORDERS ASSOCIATED WITH DOPAMINE NEUROTRANSMISSION**

Abnormalities in dopamine neurotransmission contribute to the pathogenesis of several neuropsychiatric disorders, including Parkinson’s disease, schizophrenia, drug addiction and hyperprolactinemia. Accordingly, a large number
<table>
<thead>
<tr>
<th>Dopaminergic pathway</th>
<th>Site of origin</th>
<th>Site of termination</th>
<th>Functions</th>
</tr>
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<tr>
<td>Nigrostriatal</td>
<td>Substantia nigra</td>
<td>Nucleus caudatus, putamen, globus pallidus</td>
<td>Extrapyramidal motor control</td>
</tr>
<tr>
<td>Mesocortical</td>
<td>Ventral tegmental area</td>
<td>Prefrontal, insular, motor and sensory cortices</td>
<td>Cognitive processes, motivation, encoding and use of working memory information</td>
</tr>
<tr>
<td>Mesolimbic</td>
<td>Ventral tegmental area</td>
<td>Limbic cortices, hippocampus, nucleus accumbens and amygdala</td>
<td>Reward and reinforcement mechanisms. Motivational, emotional, contextual and affective influence on behavioral processes</td>
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<tr>
<td>Tuberoinfundibular</td>
<td>Periventricular nucleus Arcuate nucleus</td>
<td>Median eminence</td>
<td>Inhibition of prolactin secretion</td>
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<tr>
<td>Incerto-hypothalamic</td>
<td>Zona incerta, posterior hypothalamus</td>
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<td>Autonomic and neuroendocrine responses</td>
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<tr>
<td>Periventricular</td>
<td>Periaqueductal and periventricular grey, dorsal motor nucleus of the vagus nerve, nucleus tractus solitarius</td>
<td>Periventricular and periaqueductal gray, tegmentum, tectum, thalamus, hypothalamus</td>
<td>Autonomic function. Control of emesis</td>
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<td>Diencephalospinal</td>
<td>Dorsal and posterior hypothalamus</td>
<td>Intermedio-lateral cell columns of spinal cord</td>
<td>Sensorimotor integration and nociception</td>
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<td>Olfactory bulb</td>
<td>Periglomerular cells</td>
<td>Glomeruli (mitral cells)</td>
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</tr>
<tr>
<td>Retina</td>
<td>Interplexiform cells</td>
<td>Inner and outer plexiform layers of retina</td>
<td>Light adaptation</td>
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Figure 1  Major dopaminergic pathways

Figure 2  Simplified basic dopaminergic regulatory scheme of forebrain structures and basal ganglia. The ventral tegmental area projects to the prefrontal, insular, motor and sensory cortices (mesocortical pathway) and to the limbic cortices, hippocampus, amygdala and ventral striatum, including the nucleus accumbens (mesolimbic pathway). The substantia nigra projects to the dorsal striatum, including nucleus caudatus and putamen (nigrostriatal pathway). Dopamine binds to D$_1$-like receptors, which stimulate second messenger systems, or D$_2$-like receptors, which inhibit second messenger systems. Dopamine neurotransmission itself is stimulated by glutamate and inhibited by GABA, with further modulatory roles of serotonin, acetylcholine, tachykinin neuropeptides, and several others.
of well-established direct dopaminergic treatments are available, that either support the actions of dopamine (precursors and agonists) or inhibit dopaminergic activity (full or partial antagonists), depending on the disease. However, these drugs currently have only limited efficacy in alleviating the symptoms of these disorders, but adverse side effects can be debilitating. Thus, there is still a considerable need for new drugs with improved therapeutic windows or more selective modes of action.

**Parkinson’s disease**

The pathological hallmark of Parkinson’s disease is a selective loss of dopaminergic neurons from the pars compacta of the substantia nigra, which leads to symptoms such as limb resting tremor, bradykinesia, rigidity, postural instability and gait disorder. Restoration of dopamine levels is the primary aim of pharmacotherapy. The dopamine precursor L-dopa (levodopa) is currently the most effective and preferred treatment. Aromatic L-amino acid decarboxylase (AAAD) inhibitors, such as carbidopa, are usually added to inhibit peripheral metabolism of levodopa. Also, dopamine receptor agonists such as pergolide, bromocriptine, apomorphine, pramipexole and ropirinol, are often used.

However, not all features of Parkinson’s disease are adequately alleviated by levodopa or dopamine agonists and patterns of response can change over time. Motor complications are frequent and disabling, and include dyskinesia and motor fluctuations (wearing off, on-off phenomena).

**Schizophrenia**

The involvement of dopamine in the pathophysiology of schizophrenia was originally suggested by the observation that dopamine-enhancing drugs can have psychotogenic effects and also by the correlation between D₂ receptor blocking potency of antipsychotic drugs and their dosage for clinical antipsychotic effect. It has been suggested that mesocortical dopaminergic projections to the prefrontal cortex might be hypoactive (resulting in hypostimulation of D₁ receptors and emergence of negative symptoms and cognitive impairments), while subcortical mesolimbic dopaminergic projections might be hyperactive (resulting in hyperstimulation of D₂ receptors and emergence of positive symptoms). A recent hypothesis proposes that the locus of dopamine dysregulation is primarily at the presynaptic level. Pharmacological treatment options include first generation antipsychotic drugs (also known as classic or typical antipsychotics) such as chlorpromazine and haloperidol. Side effects related to dopamine blockade in the extrapyramidal system include dystonia, akathisia, bradykinesia, tremor and tardive dyskinesia. In addition, hyperprolactinemia can result from dopamine blockade in the
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Tuberoinfundibular dopaminergic pathway\textsuperscript{44,45}. Other side effects include prolonged QT interval and torsade de pointes arrhythmia, related to off-target effects on cardiac potassium channels\textsuperscript{46}, and neuroleptic malignant syndrome. Second-generation antipsychotic drugs (also known as atypical antipsychotics), such as clozapine, risperidone, quetiapine, olanzapine, ziprasidone, aripiprazole and amisulpride, generally have a lower risk of extrapyramidal symptoms and tardive dyskinesia\textsuperscript{47-49} and may also be effective against negative symptoms, but can cause metabolic syndrome\textsuperscript{50}. Meta-analyses and large clinical trials have demonstrated either roughly similar clinical efficacy or moderate superiority of second-generation drugs compared with first-generation antipsychotic drugs\textsuperscript{51-58}. Clozapine has superior clinical efficacy in treatment-resistant schizophrenia\textsuperscript{59}, and carries a lower risk of extrapyramidal symptoms or hyperprolactinemia, but also has an increased incidence of agranulocytosis, requiring frequent monitoring of leukocyte counts. The exact mechanism of action of antipsychotic drugs is unknown, but all clinically effective antipsychotic drugs have been shown to attenuate dopamine $D_2$ receptor function\textsuperscript{33,38,60,61}.

**Substance abuse and drug addiction**

A large body of evidence indicates that the mesolimbic dopaminergic pathway is one of the major neuronal circuits involved in the acute rewarding effects of drugs of abuse\textsuperscript{62-66}. Although addictive drugs interact with many different neurotransmitter systems, most addictive drugs ultimately cause an acute increase in synaptic dopamine in the nucleus accumbens and mesolimbic dopaminergic system\textsuperscript{67-69}, as demonstrated by microdialysis studies in rats\textsuperscript{70} and positron emission tomography (PET) studies in humans\textsuperscript{71-75}. Alcohol, nicotine, opiates, cocaine, amphetamine (and derivates such as methamphetamine, methylphenidate and MDMA, also known as ecstasy), benzodiazepines and barbiturates all increase dopamine transmission in the mesolimbic pathway by various mechanisms\textsuperscript{76-78}. However, although addictive drugs initially lead to dopamine release in the nucleus accumbens (i.e. signaling reward), with repeated administration and as habits develop, increases of dopamine become associated with conditioned responses linked with administering the drugs, rather than the pharmacological effects of the drug per se\textsuperscript{15,79}. In addicted subjects, the drug-induced dopamine release in the striatal regions becomes significantly reduced, while conditioned cues associated with drug use increase dopamine levels\textsuperscript{15,79}. Despite the major role of dopamine neurotransmission in drug addiction, no dopaminergic agents have yet been demonstrated to be uniformly effective for substance abuse, which may be (at least partly) due to lack of selectivity for the mesolimbic pathway\textsuperscript{80}. Thus, current pharmacotherapeutic strategies primarily aim to desensitize or partially antagonize the reward system by interacting
with other neurotransmitter systems. Current treatments for alcohol abuse include the opioid-antagonists naltrexone and nalmefene, the glutamate receptor modulator acamprosate, and sensitizers to the adverse effects of ethanol like disulfiram and calcium carbimide\textsuperscript{77,80,81}. Current treatments for nicotine abuse include cholinergic drugs like the partial nicotinic acetylcholine receptor agonist varenicline and nicotine-replacement therapy, or monoaminergic therapy such as the dopamine- and norepinephrine-reuptake inhibitor bupropion, the tricyclic antidepressant nortriptyline and the $\alpha_2$ adrenergic agonist clonidine\textsuperscript{77}. Therapies for heroin addiction include the opioid agonists methadone and levo-$\alpha$-acetylmethadol, the partial agonist buprenorphine combined with naloxone, and the opioid antagonist naltrexone\textsuperscript{77,80}. No effective pharmacotherapeutic options for addiction to cocaine, cannabis, methamphetamine or other stimulants exist\textsuperscript{77,80}.

\textbf{Hyperprolactinemia}

Dopamine neurotransmission is also involved in the pathophysiology of hyperprolactinemia. Hyperprolactinemia can result from a large variety of disorders, including prolactin-secreting pituitary tumors (prolactinomas), lesions to the hypothalamus and pituitary gland that interfere with neuroendocrine control mechanisms, as well as diseases that can lead to decreased clearance of prolactin, such as liver cirrhosis and chronic renal failure\textsuperscript{82,83}. Hyperprolactinemia can also be caused by use of certain drugs. The most common drugs that cause hyperprolactinemia are drugs that inhibit dopamine neurotransmission, such as dopamine D\textsubscript{2} receptor antagonists (e.g. antipsychotic drugs and domperidone)\textsuperscript{44,45,84}. Pharmacological treatment of prolactinomas include dopamine receptor agonists, such as bromocriptine, cabergoline and quinagolide, whereas management of drug-induced hyperprolactinemia includes dose reduction of the causative drug or switching to a different drug with lower potential for prolactin elevation, if this can be achieved safely\textsuperscript{83,85,86}.

\textbf{Emesis}

Finally, dopaminergic neurons in the area postrema and nucleus tractus solitarius are involved in the control of emesis\textsuperscript{7,19}. Neurocircuitry in the area postrema and nucleus tractus solitarius involves many neurotransmitters\textsuperscript{87}, but dopamine, serotonin and the tachykinin neuropeptide substance P are thought to play the largest roles\textsuperscript{88}. Accordingly, several dopamine D\textsubscript{2} receptor antagonists (including metoclopramide, domperidone and olanzapine), serotonin 5-HT\textsubscript{3} receptor antagonists, as well as the tachykinin NK\textsubscript{1} receptor antagonist aprepitant, have demonstrated antiemetic efficacy\textsuperscript{87,89,90}.  

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STRATEGIES FOR IMPROVEMENT OF DOPAMINERGIC PHARMACOTHERAPY

In this thesis, several pharmacological strategies are presented that aim to improve dopaminergic pharmacotherapy by allowing more subtle manipulations of dopaminergic systems. Several early phase clinical trials are described that are part of larger drug development programs which explore various strategies, including improvement of receptor kinetics and receptor selectivity, as well as targeting dopaminergic control mechanisms as a means to indirectly modulate dopamine neurotransmission.

**Improvement of receptor kinetics**

It has been proposed that competitive receptor antagonists that dissociate quickly from the receptor (i.e. a fast \( k_{\text{off}} \) constant) are more accommodating to physiological fluctuations of endogenous ligand concentrations (i.e. dopamine) than drugs with a slow \( k_{\text{off}} \). Fast dissociation might therefore allow for a drug effect to occur with an appropriate functioning of physiological systems and a substantially lower risk for side effects associated with persistent strong activity at the receptor. This pharmacological concept was originally proposed to explain the differential effects of typical and atypical antipsychotic drugs, but was later criticized because several exceptions were identified. Although the fast dissociation hypothesis may thus not fully qualify as a general model for atypical antipsychotic drug action, it does provide a theoretical way to achieve reduction of side effects and may thus serve as a strategy for novel drug development. Using receptor dissociation rates as a means to screen novel compounds for antipsychotic drug candidates, the novel fast dissociating dopamine D\(_2\) receptor antagonist JNJ-37822681 was developed. In CHAPTER 2, the pharmacokinetics and central nervous system (CNS) effects of JNJ-37822681 in healthy volunteers are described. In CHAPTER 3, the binding characteristics of JNJ-37822681 in vivo are investigated using positron emission tomography (PET) and the radioligand \(^{11}\text{C}\)raclopride to evaluate if JNJ-37822681, despite its high dissociation rate, is able to achieve significant levels of dopamine D\(_2\) receptor occupancy.

**Improvement of receptor selectivity**

Increased receptor selectivity may minimize side effects related to drug action at receptor sites other than the primary target. Despite the major role of dopamine neurotransmission in the acute rewarding effects of addictive drugs, no dopaminergic agents have been demonstrated to be uniformly effective for
drug addiction, which may be (at least partly) due to lack of pharmacological and functional selectivity for the mesolimbic pathway, as well as poor tolerability. It has been suggested that selective dopamine D₃ receptor antagonism may be an effective strategy in pharmacotherapy of addiction. Preclinical models have shown that selective dopamine D₃ receptor antagonists do not affect the primary reinforcing effects of drugs of abuse, but can influence the motivation to self-administer drugs under certain schedules of reinforcement. In addition, selective dopamine D₃ receptor antagonists appear to disrupt the responsiveness to drug-associated stimuli that play a key role in reinstatement of drug-seeking behavior triggered either by re-exposure to the drug itself, re-exposure to environmental cues that had been previously associated with drug-taking behavior, or stress. Thus, selective dopamine D₃ receptor antagonists might be efficacious in decreasing craving and preventing relapse. GSK598809 is a novel selective dopamine D₃ receptor antagonist. Chapter 4 describes the pharmacokinetics and central nervous system effects of GSK598809. In addition, possible interactions between GSK598809 and alcohol were evaluated. Evaluation of interactions with alcohol is important for candidate drugs for pharmacotherapy of addiction, because the target population of patients will have substance dependence as primary disorder, and are thus likely to co-administer prescription drugs together with alcohol and other drugs of abuse.

Modulation of the tachykinergic control of dopamine neurotransmission

An alternative to direct pharmacological modulation of dopamine neurotransmission is modulation of the control mechanisms of dopamine neurotransmission. Among the many control mechanisms, the peptide neuromodulators have been proposed as suitable targets for novel drug candidates, perhaps even advantageous over antagonists to classic monamine neurotransmitters, for several reasons. First, the effects of peptide neurotransmitters are milder than those of monoamines. Second, much evidence indicates that neuropeptides are preferentially released after stressful and noxious stimuli, challenges or pathological conditions. Thus, antagonists may only act on pathophysiological systems with increased peptide release and have limited effects under normal conditions. These characteristics together might result in clinical efficacy with less pronounced side effects.

Tachykinins (also known as neurokinins) are a group of related peptide neurotransmitters that includes substance P, neurokinin A and neurokinin B. Tachykinins control and activate dopaminergic neurons in all major dopaminergic pathways, including substantia nigra, ventral tegmental area and
hypothesis. Tachykinins interact with three types of receptors, the neurokinin 1 (NK₁), neurokinin 2 (NK₂) and neurokinin 3 (NK₃) receptor, all of which are G protein-coupled receptors. The three tachykinin receptors are recognized with moderate selectivity by the endogenous tachykinins. Substance P shows the highest affinity for the NK₁ receptor, neurokinin A exhibits the highest affinity for the NK₂ receptor and neurokinin B has the highest affinity for the NK₃ receptor. Several clinical trials have evaluated tachykinin receptor antagonists for possible antipsychotic activity. Results of an exploratory clinical trial with the NK₁ receptor antagonist aprepitant in schizophrenia patients demonstrated no significant antipsychotic efficacy. In addition, despite an early positive clinical trial with osanetant, most clinical trials with the NK₃ receptor antagonists osanetant, talnetant and AZD2624 did not demonstrate convincing antipsychotic efficacy, although suboptimal pharmacokinetic characteristics of osanetant and talnetant may partly account for their poor efficacy.

Recently, interest in tachykinins has focused on a potential role in the treatment of drug addiction and substance abuse disorders. Substance P may play a role in addiction-related behavior by acting directly on NK₁ receptors in brain areas associated with drug reward, such as the nucleus accumbens and ventral pallidum, and on dopaminergic neurons in the ventral tegmental area, but also by influencing other neurotransmitters such as serotonin, acetylcholine and noradrenalin. Therefore, it has been suggested that NK₁ receptor antagonists may modulate stress- and reward-related processes and may contribute in altering drug reward. Chapter 5 describes the pharmacokinetics and central nervous system effects of the NK₁ receptor antagonist aprepitant. Also, possible interactions between aprepitant and alcohol were evaluated. To confirm and to extend the findings obtained with aprepitant, the hypothesis that tachykinin receptor antagonists may alter drug reward was investigated further. Chapter 6 describes the pharmacokinetics and central nervous system effects of GSK1144814, which has antagonist action at both NK₁ and NK₃ receptors, in a subgroup of alcohol-intoxicated volunteers, to evaluate if dual tachykinin receptor antagonism can modulate the CNS effects of alcohol.

**Modulation of the GABAergic control of dopamine neurotransmission**

GABA is one of the major inhibitors of dopamine neurotransmission (see Figure 2). Accordingly, drugs that modulate GABA neurotransmission may indirectly influence dopamine neurotransmission. Indeed, the GABA_B receptor agonist baclofen has demonstrated promising results in the treatment of...
alcohol addiction, probably by inhibiting activity of the mesolimbic dopaminergic pathway through activation of GABA_B receptors in the ventral tegmental area^{118,119}. Modulation of the GABAergic control of dopamine neurotransmission has also been suggested to underlie the therapeutic potential of benzodiazepines in the treatment of schizophrenia^{120}. Benzodiazepines were proposed to exert antipsychotic effects because of their agonist effects on GABAergic inhibition of dopamine neurotransmission^{120}. However, although the sedative and anxiolytic effects of benzodiazepines can be useful in the clinical management of acutely agitated patients, no significant effects on more specific psychotic manifestations of schizophrenia have been demonstrated^{121}.

Benzodiazepines are nonselective allosteric modulators of α₁, α₂, α₃ and α₅ subunit-containing GABA_A receptors^{122}. Recently, studies in animal models have suggested that GABA_A receptor subtypes are associated with different aspects of GABAergic drug action, like sedation (α₁ subtype), anxiolysis (α₂ and α₃ subtypes) and memory impairment (α₅ subtype)^{122,123}. Although GABA generally causes a reduction of dopaminergic neuronal activity^{21}, benzodiazepines have been shown to increase dopamine levels in the mesolimbic pathway^{76}. This increase probably results from serial inhibition of coupled GABAergic interneurons in the mesolimbic pathway, which leads to disinhibition of dopaminergic neurons, which outweighs the direct inhibitory influence of benzodiazepines on those dopaminergic neurons^{123-125}. The disinhibition of dopaminergic neurons and the resulting increase in dopamine levels appears to be mediated by the α₁ receptor subtype^{124,125}. It has been suggested that selective agonists at α₃ receptor subtypes without efficacy at α₁ receptor subtypes, may attenuate dopamine neurotransmission in the mesolimbic pathway, without counteractive disinhibition from GABAergic interneurons^{123}. Accordingly, GABA_A receptor subunit-selective agonists may differ significantly from nonselective benzodiazepines in their effects on dopaminergic pathways, and may have therapeutic potential for (some aspects of) schizophrenia^{123}.

A targeted selection of the proper subtype-selective GABA_A agonist would require a good understanding of the exact role of the various receptor subtypes in the regulation of different dopaminergic activities. To explore the exact role of the various receptor subtypes in the regulation of dopamine neurotransmission, CHAPTER 7 describes the effects of two novel positive modulators of α₂ and α₃ subunit-containing GABA_A receptors, AZD7325 and AZD6280^{126}, and the nonselective benzodiazepine lorazepam on circulating prolactin levels as a marker for activity of the tuberoinfundibular pathway, which is the most readily accessible dopaminergic pathway for evaluation in vivo.
CONCLUSION AND AIM OF THESIS

The neurotransmitter dopamine is involved in the pathogenesis of several neuropsychiatric disorders. Despite the large number of registered dopamine receptor agonists and antagonists, pharmacological methods to alter dopamine neurotransmission currently have only limited efficacy in alleviating the symptoms of these disorders, while adverse side effects can be debilitating. This thesis describes early phase drug development studies that are part of larger drug development programs which explore various strategies for improvement of dopaminergic pharmacotherapy. These strategies include improvement of receptor kinetics (CHAPTER 2 AND 3) and receptor selectivity (CHAPTER 4), as well as modulation of dopamine control mechanisms (CHAPTER 5, 6 AND 7). This thesis aims to evaluate pharmacokinetics and dose-effect relationships of several drug candidates on various neurophysiological parameters in healthy volunteers in order to show penetration through the blood-brain barrier, target engagement in vivo and differentiation of pharmacodynamic effects on several functional CNS domains.
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