CHAPTER VII

Discussion

For already thousands of years, cannabis has been the most widely used illicit drug for recreational and medicinal purposes. The receptors on which cannabinoids act are part of one of the most phylogenically ancient and widely preserved pharmacological systems in biology. Nonetheless, this endocannabinoid system has only been discovered during the last few decades, and scientific progress in understanding the relevance of this system in health and disease has been limited and slow. As a result, only a few drugs that act on the endocannabinoid system have been registered, most of which are components of *Cannabis sativa*. At the end of 2006, just when cannabis research was flourishing, the industry suddenly lost its interest due to concerns of the FDA about the safety of CB_1 antagonist rimonabant, an anti-obesity drug with inverse agonistic properties. The registration of rimonabant, which was hailed as a breakthrough in drug research and in treatment of the metabolic syndrome, was quickly followed by a market withdrawal in 2008. This resulted in an almost complete and unanimous ban on CB_1 antagonist research, which is still felt today.

The demise of rimonabant reflects many of the difficulties of cannabinoid drug development. Some of these are related to public perceptions. Research on cannabinoid agents is often regarded suspiciously because of concerns of abuse. Many of the most promising potential indications for cannabinoid drugs are disputed: obesity is not considered a disease by the American Medical Association (ama Council, 2013), addiction is often viewed as an individual failure of character (Gartner et al., 2012), and many pharmaceutical industries regard psychosis as too risky for commercial drug development (van Gerven and Cohen, 2011).

The unfortunate fate of rimonabant is also related to some fundamental scientific complexities of endocannabinoid research. Some of these are mentioned in the introduction: widespread distribution, limited subtype specificity, local production of highly lipophilic and rapidly degraded transmitters, complex physiological integration, lack of good effect measures, all leading to unclear pathophysiological involvement. But the focus of endocannabinoid research on cannabis can also be misleading. Many of the putative indications for cannabinoid agonists or antagonists are inspired by the well-known effects of recreational cannabis consumption. Although feeling pleasant and 'high', getting the 'munchies', or suffering from panic attacks after using cannabis, are undoubtedly founded in the functional pharmacology of endocannabinoid systems, these effects reflect limited aspects of gross overstimulation. They hardly represent the local functions of endocannabinoids in the subtle regulatory modulation of normal physiological processes, or their involvement in intercellular or systemic derangements of complex multicascadic functional networks.

The failure of rimonabant also reflects some weaknesses of current drug development. Rimonabant was considered a 'miracle drug' for the treatment of obesity and smoking (Boekholdt and Peters, 2010), with 'blockbuster' potential. Its development was based on the 'logical' notion that blocking hunger or reward (and associated physiological processes) will reduce weight and craving (i.e. induce the opposite of cannabis-associated munchies and abuse). But it was disregarded that along the same reasoning, inhibition of pleasant feelings (i.e. inverse of cannabis-induced euphoria) would be expected to have a negative impact on mood. Nonetheless, to the best of our knowledge, emotional or cognitive effects have never been studied systematically in clinical trials. There seems to have been no systematic evaluation of the balance of the inferred beneficial and detrimental effects of rimonabant, which would be essential for the determination of a therapeutic window.

In this thesis, we explore some improvements in the early development of cannabinoids, by systematically investigating new cannabinoid compounds and formulations to enhance their pharmacological activities, experimenting with new methodology to optimise effect measurement, and applying new concentration-effect models to improve the simulation and prediction of future studies.

IMPROVING PHARMACOLOGY

In Chapter 2 we investigated the pharmacology of different administration methods of Namisol® THC tablets, which are based on an improved emulsifying technology to enhance absorption. Somewhat unexpectedly, we have found that oral administration resulted in a quicker THC absorption into the blood compartment compared to sublingual administration of a crushed tablet and we suggested that the absorption via oromucosal tissue is relatively slow compared to gastrointestinal absorption. If we compare our results to the findings from THC inhalation studies (e.g. from Chapter 3, 4 and 5), the proportion of active metabolite (11-OH-THC) to THC is larger for the oral administration, meaning that relatively more active metabolite is formed than after inhalation. Compared with the literature on other oral THC formulations, Namisol® seems to have a shorter absorption time (or T_{MAX}) with reduced variability, probably contributing to a faster and more predictable onset of effects. We concluded that Namisol® seems to have benefits over common oral cannabis and THC treatments and we suggested that Namisol® offers potential improvements over currently registered cannabinoid-treatments including registered oral THC formulations. However, this would require a direct comparison of the pk and pd of the oral thc tablet Namisol® with the current registered oral, oromucosal and sublingual formulations. Also, the absolute bioavailability of the various formulations should be studied, although this would be limited by the lack of a standardised intravenous dosage.

Because the endocannabinoid system is relative inactive under physiological circumstance, cannabinoid antagonists show no acute effects under normal resting conditions. We therefore used a THC-challenge test in Chapter 4 and 5 to examine the pharmacology of new CB_1 antagonists in healthy subjects. The effects of a thc challenge test are clearly measurable in healthy subjects and we have previously demonstrated that these effects can be inhibited by CB_1 antagonists (Zuurman et al., 2010).

In Chapter 4 we investigated the pharmacokinetics of surinabant and its pharmacodynamic effects on those of THC. As a consequence of the recent rimonabant incident, we aimed to characterize the dose-effect relationships for surinabant, to support the prediction of optimal effects and minimal risk for unwanted (central) side effects in patient studies. Although surinabant exhibited no effects of its own on a wide range of different CNS-function tests, we concluded that the dose-related inhibition of THC, demonstrates unequivocal CB_1 receptor antagonism in humans. A single surinabant dose between 5 to 20 mg was able to completely antagonize THC-induced effects in humans. Higher doses were well tolerated, but did no show additional pharmacological activity. During the time of study performance we hoped that our results would allow the determination of clinically effective doses with minimised central side effects. However, shortly after our study surinabant development was ceased due to adverse psychiatric effects in phase 2. The relevant doses were determined prior to the start of our study, based on different grounds than those of our study. The plasma concentration range at which the adverse events prominently occurred were relatively high compared to our study (Sanofi, personal communication).

To improve the therapeutic window between metabolic improvements and mental disturbance, TM38837 was developed as a peripherally selective CB_1 antagonist. In rodents, this antagonist only hardly penetrates through the blood-brain barrier in dosages that show beneficial effects on metabolism. Chapter 5 describes the first study of this compound in humans. It was also the first direct comparison of two cannabinoid antagonists (TM38837 and the formerly registered rimonabant) in a clinical study, which is an efficient way to characterize new compounds. This study gave us insight into the PK and effect profiles of a peripherally acting antagonist and the differences compared to rimonabant by statistical analyses and PK and PK-PD modelling. When directly compared to rimonabant, TM38837 had a relatively large inhibiting effect on THC-induced heart rate (which had previously been argued to be a mainly pe-

ripheral effect (Zuurman et al., 2009; Strougo et al., 2008)) with relatively small effects on subjective scores associated with CNS activity (e.g. feeling high) and body sway. The lowest TM38837 dose of 100 mg was predicted to be at least equipotent to rimonabant with regard to metabolic disorders in rodent models and had no significant impact on CNS-effects in our study. These results provide support for further development of TM38837 as a peripherally selective CB_1 antagonist for indications such as metabolic disorders, with a reduced propensity for psychiatric side effects. The PK-PD analyses were put in a larger perspective in Chapter 6, in which the results from Chapter 4 and 5 and the results from a previous study with drinabant (ave1625) (Zuurman et al., 2010) were all used for building a general antagonist model. These analyses confirmed our graphical interpretation that tm38837 has a relatively larger peripheral effect than central effects when compared to rimonabant, surinabant and drinabant. We concluded that the relatively low central activity and the large effects on heart rate suggest a potential for therapeutic treatment development of tm38837, with minimal risks of the central side effects attributed to rimonabant.

OPTIMISING MEASUREMENTS

Besides the limited knowledge on the endocannabinoid system, and the pharmacology that limits the possibilities of pharmacotherapy, optimisation of drug development is limited by the lack of validated effect measurements. New techniques can be important tools to better understand the physiology of the cannabinoid system, to optimize dose selection and effect profiling, and to improve our understanding of the involvement of cannabinoid systems in general.

Since all central nervous system (CNS) functions ultimately depend on the activity of neuronal networks, connectivity analyses of neurophysiological (electroencephalography (EEG), magnetoencephalography (MEG)) or neuroimaging technologies (positron emission tomography (PET), functional magnetic resonance imaging (FMRI)) may provide useful tools for a more direct assessment of drug- or disease-induced functional CNS-changes. In Chapter 3 we measured brain connectivity changes after THC administration by using resting-state functional MRI (RS-FMRI.) We found that THC induced increases and decreases of brain connectivity for various networks of interest. These clear effects (which are also found with other medications by other members of our research group) suggested that RS-FMRI is a suitable method to apply in early clinical stages of drug development. The brain regions in which the connectivity changes were found were comparable with the functional regions that are associated with the behavioural effects after THC or cannabis use such as postural stability and altered time perception. RS-FMRI has some unique features, compared with other CNS measures that we used in this thesis. As opposed to more commonly applied neurophysiological, functional and subjective methods, RS-FMRI is able to detect a wide range of direct and indirect (acute) effects and to 'objectively' measure effect profiles, with less concealed interference from compensatory mechanisms and motivational aspects or other factors that can affect responses and performance. Moreover, this might enable early phase clinical research on compounds at low concentrations with a functional impact that can be easily compensated, or which is too limited to noticeably affect performance. RS-FMRI may also show effects of antagonists that do not induce acute measurable effects in the commonly used neurophysiologic tests, although this remains to be established.

Overall, we concluded that THC induces connectivity changes in brain regions that are comparable with the functional regions that are associated with the behavioural effects after THC or cannabis use, and that RS-FMRI is a suitable technique for clinical drug development, including development of cannabinoid pharmacotherapies. Future research could maturate the applicability of the RS-FMRI methodology by investigating dose-effect relationships, for example by developing a PK-PD model for RS-FMRI. Also, it would be interesting to understand

the implications of the methodology in a wider perspective, for example by exploring the relationships between the connectivity changes and functions. This will allow us to optimise the usability of the technique, but also to improve our understanding of the biological systems of the brain in general.

IMPROVING ANALYSES

For the analysis of Chapter 5 which describes a study with the peripherally specific CB_1 antagonist TM38837 and rimonabant in a THC-challenge test, PK-PD models were developed for heart rate, postural stability and feeling high. All PK-PD models included a baseline level, effect compartments that equilibrated with the plasma concentration, and a model to relate the effect compartment concentration to the pharmacodynamic response. Heart rate and body sway were best described by a maximum effect model. For feeling high a probability model was used to quantify the probability for a VAS score > 12 at the study population level. All models included the THC challenge effect and the antagonizing effect of rimonabant and TM38837. The equilibration half-life of TM38837 was long compared with rimonabant, causing a larger delay in the onset of TM38837 effects. For heart rate the half maximal inhibitory concentrations (IC_{50}) were similar for TM38837 and rimonabant, whereas for body sway and feeling high the IC_{50} of rimonabant was 4 times and 56 times larger respectively than for TM38837. This suggests that TM38837 induces relatively smaller central effects than peripheral effects when compared with rimonabant. The time profiles of the effects were comparable with the pharmacokinetic profiles of the compounds. Unfortunately, no therapeutic trials have been performed with TM38837 so far, to verify these predictions.

In Chapter 6 we built PK-PD models for four different CB_1 antagonists: drinabant (AVE1625), surinabant (SR147778), rimonabant (SR141716) and TM38837. This approach gave us insight in the differences of the PK and PD between the four antagonists and increased our knowledge on the behaviour of CB_1 antagonists in general. Compared to TM38837, surinabant and rimonabant effect profiles induced relatively larger centrally regulated PD effects than heart rate effects. The models can be applied for optimization as well as development of future clinical studies by simulation and prediction of the PK and PD of cannabinoid antagonists. As of today, research continues developing the mechanism-based PK-PD modelling with for example more emphasis on disease system analysis. Mechanism-based PK-PD modelling is an important field that should continue in the future. Besides the desire to develop a translational tool from healthy subjects to patients, also in other phases of drug development tools for translation, simulation and prediction of pharmacokinetics and effects could be applied (e.g. from preclinical to clinical studies).

GENERAL CONCLUSION

The aim of this thesis was to explore some ways to advance cannabinoid drug design, by improvements of study designs, measurements and analyses in early phase clinical studies. Such improvement seem to be needed to increase our understanding of the pharmacology of cannabinoids in healthy people, and enable a more effective control of the cannabinoid system in pathology.

In this thesis, we have introduced a new oral THC formulation and a new CB_1 antagonist, which we tested in healthy subjects. We concluded that the new formulations showed more beneficial pharmacological effects compared to current treatments. We have also optimized and applied new methodologies. We have provided indications that resting state FMRI is a suitable technology for early phase clinical drug development. We have also demonstrated that the THC-challenge test can be applied for pharmacological characterisation and dose optimisation of antagonists. For this, we developed PK-PD models for THC and the

CB1 antagonists drinabant, surinabant, TM38837 and inverse agonist rimonabant. These models can be applied for simulation and prediction of PK and PD, for example to optimise future study designs. These methods provide more information than the 'traditional' approaches in early development, where dose selection is essentially based on extrapolation of preclinical results, pharmacokinetic optimisation of dosing regimens, and estimation of maximum tolerated doses – at best supplemented with some indications of pharmacodynamic effects. This approach can easily fail if the investigative compound has a novel mechanism of action, and particularly when it has no effects under physiologically stable conditions. This seems to have been the case for rimonabant, which had to be withdrawn shortly after registration, because of adverse psychiatric events that perhaps in hindsight were not unexpected. We used the PK-PD-approach that is described in this thesis to determine a pharmacologically optimised dose for rimonabant as well as for other novel CB1-antagonists. This analysis suggested that rimonabant may have been overdosed, possibly because the compound is so well tolerated in healthy subjects where it has no 'spontaneous' effects. Clearly, this remains speculative as long as confirmatory studies have not been performed.

At present, there are still questions about the predictive value of the pharmacological biomarkers, for clinically relevant therapeutic or inadvertent effects of CB1-antagonists. It remains to be established, therefore, whether functional challenge studies and pharmacological PK-PD-analyses would actually allow the determination of a therapeutic window that is large enough for a safe and effective use of CB1-antagonists. Nonetheless, a pharmacological approach gives hope that drug development in the field of endocannabinoids is feasible and potentially useful, despite the many problems that are inherent to this complex system. The hope for cannabinoid research and drug development may also be fuelled by the break-down of taboos on cannabis use. The recreational use of cannabis gradually gained more acceptance since the 1970's, and an increasing number of countries and states in the USA have decriminalised cannabis [(Robison, 2013) for visualisation, see Reeve (2013)]. The spread of cannabis use, particularly for medical purposes also increases general social acceptance and stimulation of further research of cannabis-related compounds.

OVERALL CONCLUSIONS

Our results lead to the conclusion that there is room for improvement in cannabinoid research – enough to give confidence that the cannabinoid system still has potential as a target for pharmacological therapies, despite the setback after the market withdrawal of the first registered cannabinoid antagonist shortly after launch. Although the current amount of cannabinoid research is relatively low, and clinical research is particularly limited, the social acceptance of cannabis, also as a medicine, could facilitate a revival of research on the cannabinoid system. Our research shows that this requires novel approaches to the administration of cannabinoids, to the measurements and the study designs, and to the analyses of the effects. This reflects the complexity of the highly integrated endocannabinoid system, but also sets the stage for other innovative drug development programs.

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