Abstract

This thesis describes in the form of a commentary on own original publications research on the problems of cannabinoids, ie. phytocannabinoids and some synthetic cannabinoids, their pharmacokinetics and effects.

The work consists of four thematic areas: the pharmacokinetics of delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) in rats, depending on the route of administration; THC concentration time profile in humans (after inhalation) and implications for transport safety; the pharmacokinetic profile of synthetic cannabinoids in rats; extraction and determination of phytocannabinoids in plant material.

The first part of the thesis was to determine pharmacokinetic profiles of THC, CBD and combination thereof (1:1 weight ratio) in rats with respect to administration common in humans, i.e. inhalation, oral and subcutaneous administration. THC, its metabolites (11-hydroxy-tetrahydrocannabinol, 11-OH-THC; 11-nor-delta-9-carboxytetrahydrocannabinol, THCOOH) and CBD concentrations in serum and brains of animals were monitored at the 24 hours experimental interval during the study. Except for inhalation administration, co-administration of CBD inhibited THC metabolism (after both oral and subcutaneous), resulting in an increase in THC concentrations in both serum and brain of the rats relative to THC alone. The surprising result of the study was that after oral and subcutaneous administration of CBD alone, THC was measured in both the serum and brain of experimental animals – it is an in vivo confirmation of previous in vitro experiments documenting the conversion of CBD to THC. The results of this work bring new findings for possible new drug formulations of cannabinoids, especially in terms of possible metabolic interactions. The in vivo conversion of CBD to THC itself will be the basis for further research in this field, especially with regard to therapeutic use of cannabidiolic preparations by humans and also with respect to the forensic evaluation of psychotropic substances

The second section focused on monitoring THC levels in recreational and chronic cannabis users. The follow-up interval was immediately after the usual inhalation dose of the drug, i.e. one cigarette / joint, until 24 hours after application. Our studyconfirmed the results of earlier controlled kinetic studies that THC is not detectable in recreational users with common instrumental equipment as early as 4 hours after use, while in chronic users

is THC detectable even after more than 24 hours of abstinence. In this context, it should be emphasized that many chronic users had basal THC levels from recent use before the start of the experiment, due to the redistribution of THC from lipophilic depots to blood. Consumption of cannabis has an individual influence on the cognitive and psychomotor abilities of the user. The practical forensic question remains how long the psychotropic effects of THC can persist in chronics after the last dose of the drug and after persistent abstinence. Cases of long-term adverse effects on neurocognitive functions are documented in chronic users. Thus, the THC blood level in drivers does not in itself have to correlate directly with the degree of influence on central nervous system. Therefore, in a number of countries, per se legislation based on an analytical principle with minimal tolerance to drugs in the driver's blood was introduced for preventive reasons and in an effort to reduce traffic risks, including THC. The distinction between acute and chronic cannabis consumption in assessing safety risks, especially in traffic, is still the subject of many studies.

The third section was devoted to comparing the pharmacokinetics of new synthetic cannabinoids (SK) and THC following subcutaneous administration to experimental rats. Synthetic cannabinoids are substances originally developed for research and modulation of the endocannabinoid system, but in recent years they have largely appeared on the drug market as they mimic the effects of natural cannabinoids. The SKs studied are indole derivatives (JWH-073 and JWH-210). These are lipophilic and very potent substances with high affinity for endogenous cannabinoid CB1 and CB2 receptors, and in this respect their recreational use is associated with a high incidence of adverse events. Pharmacokinetic profiles of JWH-073, JWH-210 and THC in rat serum were determined at 24 hours interval. In the SKs studied, different pharmacokinetic profiles were observed with respect to THC, presumably with regard to their different lipophilicity and hence subsequent blood redistribution. JWH-210 showed a biphasic profile with two concentration maxima, analogous to subcutaneous administration of THC, while JWH-073 peaked up to 4 hours after administration. The time course of the studied substances established in our work correlates with the published data, which shows the consistency of our findings.

The last section was devoted to the extraction of phytocannabinoids from plant material, namely from the inflorescence of Cannabis sativa. Extraction of

phytocannabinoids (and their determination) is important not only for the forensic monitoring of THC potency in seized plant material, but with the progress of medical use of marijuana also for the determination of individual cannabinoid distribution in particular varieties with respect to their therapautic indications. In this regard, organic solvent extraction processes are widespread, but they are often toxic, with respect to the environment and human health. Therefore, a series of alternative deep-eutectic solvents (DES) based on non-toxic starting materials, in this case terpenes and natural organic acids, were prepared and their extraction efficiency tested for selected phytocannabinoids (THC, CBD and their carboxylated homologs). Eutectic liquid based on menthol and acetic acid reached the highest extraction efficiency, not only between the tested DES, but mainly compared to the often used methanol/chloroform extraction mixture, where higher yields of up to tens of percent were reached. Due to the encouraging results of this pilot study, eutectic liquids can be used not only in the field of green analytical chemistry, but they also have potential for the pharmaceutical industry (eg. tinctures of cannabinoids based on these liquids).