INTRODUCTION
Among the ~110 cannabinoids isolated from hemp (Cannabis sativa), δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD) have been the most thoroughly studied substances. Synthetic THC has been available for three decades as a medicine, and pharmaceutical grade herbal cannabis as well as formulations of cannabis extracts containing THC and CBD in well-defined ratio have also been registered as medicines in several countries.1

Cannabidiol (Fig. 1), one of the major ingredients of C. sativa, was first isolated from American hemp2 and Egyptian hashish3 in 1940. Its structure was determined by Mechoulam & Shiin 1963.4 Historical, preclinical laboratory and human case reports as well as a plethora of anecdotal accounts combined with the relative safety of CBD prompted the exploration of the therapeutic potential of CBD against a range of diseases.5,6 The promise of CBD in treating drug-resistant epilepsy in children has recently brought this natural product into the focus of the scientific community, the media as well as politicians and regulatory bodies, in particular in the USA.7,8,9

The chemistry, pharmacology of CBD and the various molecular targets this non-psychotropic cannabinoid interacts with have been reviewed.10 Some information on the pharmacokinetics of CBD in experimental animals and humans is also available.11–13 However, unlike the parent compound, the biological activity of CBD metabolites has received less attention. A recent review summarized the biological properties of the main THC metabolite.2 This poster reviews the pharmacokinetics of CBD and the scarce information on the biological properties of its metabolites.

HUMAN PHARMACOKINETICS OF CBD UPON VARIOUS ADMINISTRATION ROUTES
Due to extensive Phase I metabolism, the pharmacokinetics of CBD is complex and the bioavailability of oral CBD is low across species.12 In general, the most abundant metabolites are water-soluble hydroxylated 7-COOH derivatives (Fig. 2) that are excreted either intact or as glucuronide conjugates. The route of administration affects the pharmacokinetics of CBD and, in humans, high intra- and inter-subject variability is not unusual. It is of note that a large portion of the administered CBD is excreted intact or as its glucuronide.

In individuals smoking of a single cigarette containing ~19 mg CBD, average peak blood plasma level was 110 ng/ml (at 3 min post-dose), the half-life was ~31 h, and the systemic availability was estimated as 31% (range: 10–42 ng/ml; n = 5).23

An early study using intravenous injection of 20 mg [14C]CBD observed that 33% of the total radioactivity, mostly unchanged CBD accompanied by several oxygenated metabolites (TLC), was excreted in the feces in 72 h.24 A more detailed investigation found that intravenous injection of 20 mg CBD resulted in peak plasma level of 686 ng/ml (at 3 min post-dose) that rapidly dropped to 48 ng/ml at 1 h; the half-life was ~24 h and bioavailability was estimated to be 6%.23

Oral administration of a blend of 40 mg CBD + 20 mg THC resulted in low peak plasma levels of ~5 ng/ml for each drug at 1.5–3 h.25 Similar low peak plasma levels (range 0.3–2.6 ng/ml) were noted in Fig. 2 at 1 h after oral ingestion of a cannabis extract containing 5.4 mg CBD and 10 mg THC.26 Chronic administration of large doses of CBD does not result in elevated mean blood concentrations: in a 6-week trial using daily oral doses of 700 mg CBD, plasma levels of the drug remained in a low, narrow range of 6–11 ng/ml throughout the trial and the elimination half-life was 2–5 days.27 A recent study recorded respective mean blood concentrations of 4.7 and 17 ng/ml of CBD after 1 and 2 h oral intake of a single dose of 600 mg CBD.28 Peak plasma CBD concentrations as high as 221 ng/ml 3 h after concomitant oral administration of 800 mg CBD + 1 mg/kg fentanyl (i.v.) have been reported.29

As a part of an extensive series of studies of cannabis based medicine extracts (e.g., Sativex®) the pharmacokinetics of a total dose of 20 mg CBD in sublingual drops was studied.30 The highest plasma concentration was 2 ng/ml at 120 min post-dose. Similar values were obtained for a 1:1 mixture of THC:CBD applied either in sublingual drops or as aerosol: when applied via a nebuliser (10 mg THC + 10 mg CBD), however, the peak plasma level was 9.5 ng/ml at 36 min and the half-life was 66 min. Upon oromucosal application of low (5.4 mg THC + 5.0 mg CBD) and high (16.2 mg THC + 15.0 mg CBD) Sativex® doses, the mean peak plasma levels were 1.6 ng/ml at 3.7 h and 6.7 ng/ml at 4.0 h, respectively.31,32

The human skin permeation of CBD solutions was investigated in vitro33 and various CBD-formulations for transdermal and intranasal administration have been studied also in rodents.34,35

According to an analysis of in vivo distribution of cannabinoids in post-mortem cases, high CBD concentrations were found in bile (up to 63 ng/ml) and muscle (up to 32 ng/g) tissues; the relatively high CBD-content of the brain (up to 6 ng/g) was unexpected.33,36,37

CANNABIDIOL METABOLITES: FORMATION AND BIOLOGICAL ACTIVITY
An overview of the literature
István Ujváry, iKem BT, Budapest, Hungary

HUMAN METABOLISM OF CBD
Since the first identification from rat liver homogenate of 7-OH-CBD and 3'-OH-CBD (for numbering, see Fig. 1) in 1973,38 cannabinoid studies in mammals, including humans, using various types of administrations indicated considerably species variability. Being a good substrate of cytochrome P450 (CYP450) mixed function oxidases, CBD undergoes extensive hydroxylation at multiple sites and further oxidations result in complex metabolic profiles; altogether some 100 CBD metabolites have been identified.39 Compared to THC, the metabolism of CBD is unusually complex. The major metabolites of CBD were derivatives of CBD-7-oxic acid hydroxylated at the side chain.

Following initial excretion studies,40-42 about 40 oxygenated Phase I metabolites / biotransformation products have been characterized typically in human urine (Fig. 2).19,43-52 The structures of main metabolites, identified in the urine of a dystonic patient chronically treated with 5 mg daily oral doses of CBD are shown in Fig. 2. Minor metabolites found in the urine were produced by human in vitro are listed in Fig. 2b. (The concentration of CBD was 12.1% of the total excreted cannabinoids.)

Of the various CYP450 isoforms, CYP3A4 and CYP2C19 appear to be the main isoforms responsible for the formation of 6-OH, 7-OH and 4'-OH CBD metabolites, while CYP1A and CYP3A isoforms are involved in the 1'- and 2'-hydroxylations of CBD.42 Glucuronidation of CBD at the phenolic oxygen at 1'-position is a major Phase II metabolic step in humans.38,44-51

Fig. 1. The chemical structure of CBD

Fig. 2a. Chemical structures and abbreviations of major (>1%) human metabolites of CBD (numbering as in Fig. 1)

Fig. 2b. Abbreviated names of minor (>1%) or trace human metabolites of CBD (numbering as in Fig. 1)

Fig. 3. Chemical structures of potential human metabolites of CBD (see text for explanation)
In vitro were be as a new metabolite of cannabidiol in mammals.


