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ORIGINAL ARTICLE

Conversion of cannabidiol to Δ^9-tetrahydrocannabinol and related cannabinoids in artificial gastric juice, and their pharmacological effects in mice

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Abstract Cannabidiol (CBD), a nonpsychoactive cannabinoid, was found to be converted to 9α-hydroxyhexahydrocannabinol (9α-OH-HHC) and 8-hydroxy-*iso*-hexahydrocannabinol (8-OH-*iso*-HHC) together with Δ^9-tetrahydrocannabinol (Δ^9-THC), a psychoactive cannabinoid, and cannabinol in artificial gastric juice. These cannabinoids were identified by gas chromatography-mass spectrometry (GC-MS) by comparison with the spectral data of the authentic compounds. Pharmacological effects of 9α-OH-HHC and 8-OH-*iso*-HHC in mice were examined using catalepsy, hypothermia, pentobarbital-induced sleep prolongation, and antinociception against acetic acid-induced writhing as indices. The ED_{50} values (effective dose producing a 50% reduction of control; mg/kg, i.v.) of 9α-OH-HHC and 8-OH-*iso*-HHC for the cataleptogenic effect were 8.0 and 30.4, respectively. 8-OH-*iso*-HHC (10 mg/kg, i.v.) produced a significant hypothermia from 15 to 90 min after administration, although 9α-OH-HHC failed to induce such an effect at the same dose. However, both HHCs (10 mg/kg, i.v.) significantly prolonged pentobarbital-induced sleeping time by 1.8 to 8.0 times as compared with the control solution with 1% Tween 80-saline. The ED_{50} values (mg/kg, i.v.) of 9α-OH-HHC and 8-OH-*iso*-HHC for the antinociceptive effect were 14.1 and 39.4, respectively. The present study demonstrated that CBD can be converted to Δ^9-THC and its related cannabinoids, 9α-OH-HHC and 8-OH-*iso*-HHC, in artificial gastric juice, and that these HHCs show Δ^9-THC-like effects in mice, although their pharmacological effects were less potent than those of Δ^9-THC.

Keywords Cannabidiol · Δ^9-Tetrahydrocannabinol · 9α-Hydroxyhexahydrocannabinol · 8-Hydroxy-*iso*-hexahydrocannabinol · Acid-catalyzed cyclization · Antinociceptive effect

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Introduction

Cannabidiol (CBD), which is one of the major cannabinoids in marijuana, is known to be devoid of psychoactivity in humans [1–3]. In chemical reactions, the acid-catalyzed conversion of CBD to other cannabinoids is well documented. Many years ago, Adams et al. [4,5] reported that CBD was converted to cannabinoids possessing marijuana-like pharmacological effects under various acidic conditions; at that time, however, a precise structure of CBD was not established [4]. Thereafter, Gaoni and Mechoulam [6,7] reported that CBD was easily isomerized in a number of acidic reagents including hydrochloric acid and *p*-toluenesulfonic acid to give various cannabinoids. It is very important to know whether CBD is converted to Δ^9-tetrahydrocannabinol (Δ^9-THC) during the handling of marijuana and in biological systems. However, there are few reports on the

conversion of CBD to other cannabinoids in biological systems. Quarles et al. [8] reported that CBD did not form Δ^9-THC when marijuana cigarettes were smoked either by human subjects or by a smoking machine. We previously reported that CBD was biotransformed to a THC derivative, 6β-hydroxymethyl-Δ^9-THC, via an epoxy intermediate with guinea pig hepatic microsomes [9]. 6β-Hydroxymethyl-Δ^9-THC exhibited some THC-like effects, although its effects were much less active than those of Δ^9-THC. In biological systems, there have been no reports on the conversion of CBD to Δ^9-THC itself. Marijuana can be ingested with foods or drinks, and reach the stomach, which is under strong acidic conditions containing gastric juice. For better understanding of whether CBD is converted to other cannabinoids, it is important to investigate the cyclization of CBD under conditions similar to those in biological systems. In the present study, we describe the conversion of CBD to Δ^9-THC, cannabinol (CBN), and hexahydrocannabinols (HHCs) in artificial gastric juice and their pharmacological effects in mice.

Materials and methods

Materials

Δ^9-THC, CBD, and CBN were isolated and purified from cannabis leaves by the methods of Aramaki et al. [10]. 8-Hydroxy-*iso*-HHC (8-OH-*iso*-HHC) and 9α-hydroxy-HHC (9α-OH-HHC) were prepared by the methods of Gaoni and Mechoulam [7] and Petrzilka et al. [11], respectively. The purities of these cannabinoids were checked to be more than 98% by gas chromatography (GC). Other chemicals and solvents used were of the highest purity commercially available.

Conversion of CBD in artificial gastric juice

CBD (250 μg) was incubated in 5 ml of a modified artificial gastric juice without pepsin (2 mg/ml NaCl solution, pH 1.2) (*Japanese Pharmacopoeia* 14th Edn, 2001) at 37°C for 20 h. The mixture was extracted twice with 20 ml of ethyl acetate after addition of 5α-cholestane (5 μg) as internal standard (IS). After evaporation of the organic solvent, the residue was dissolved in 250 μl of ethyl acetate and a 5-μl aliquot was subjected to thin-layer chromatography (TLC) with a solvent system of benzene/*n*-hexane/diethylamine (25 : 10 : 1). The cannabinoids formed from CBD were visualized by spraying 0.1% Fast Blue BB salt. Another portion (1 μl) of the ethyl acetate solution was injected into a gas chromatography-mass spectrometry (GC-MS) system.

GC-MS conditions

We used two types of GC-MS instruments. For a JEOL JMS 06 gas chromatograph coupled with a JEOL JMS DX-300 GC mass spectrometer and a JEOL DA mass data system, the conditions 1 were: column, 5% SE-30 on Chromosorb W (60–80 mesh, 3 mm × 2 m); column temperature, 260°C; ionization, 70 eV; ionizing current, 300 μA; carrier gas, He at 40 ml/min.

For a Shimadzu GCMS-QP2010 instrument, the conditions 2 were: column, DB-1 (0.25 mm × 30 m, film thickness, 0.25 μm); column temperature program, 50°C (1 min), 25°C/min (6 min), 10°C/min (10 min), and 300°C (5-min hold); ion source temperature, 250°C; interface temperature, 280°C; ionization, 70 eV; emission current, 60 μA; carrier gas, He at 2.04 ml/min.

Under the above conditions, the retention times (min; conditions 1 and 2) of cannabinoids were: CBD (3.7, 13.6), Δ^9-THC (4.7, 14.3), CBN (5.4, 14.9), 9α-OH-HHC (5.6, 15.0), 8-OH-*iso*-HHC (6.0, 15.2), and 5α-cholestane (11.2, 17.2).

Pharmacological experiments

Male ddY mice (20–25 g body weight) were used for pharmacological experiments. They were kept in an air-conditioned room (22.0° ± 2°C) with a 12-h light and dark cycle with automatically controlled lighting, and given food and water ad lib. Each cannabinoid was suspended in saline containing 1% Tween-80 and injected into mice intravenously. The pharmacological effects of the cannabinoids were evaluated by the following criteria [12,13].

1. Catalepsy: mice were separated into three groups, each of 8 animals. They were injected with different amounts of each cannabinoid, and the cataleptogenic effect was assessed by the simple bar test [12].
2. Hypothermia: five groups of mice (n = 8) were injected with each cannabinoid (10 mg/kg), and the rectal temperature of each mouse was measured using a thermister thermometer up to 120 min after the administration.
3. Pentobarbital-induced sleep: five groups of mice (n = 8–24) were injected with each cannabinoid (5 or 10 mg/kg) and challenged with sodium pentobarbital (40 mg/kg, i.p.) 15 min later. The time between the loss and the regaining of the righting reflex was recorded as the sleeping period.
4. Antinociception: antinociceptive effect was also assessed by the blockade of 0.7% acetic acid (10 ml/kg, i.p.)-induced writhing [13].

Statistical analysis

The statistical significance of difference between the control and the test groups was analyzed by use of the Bonferroni test. Differences were accepted as being significant at $P < 0.05$ or $P < 0.01$. The ED_{50} values (effective dose producing a 50% reduction of control) and their 95% confidence limits in the cataleptogenic and antinociceptive effects of cannabinoids were calculated by the method of Litchfield and Wilcoxon [14].

Results and discussion

CBD was converted to Δ^9-THC and HHCs when incubated in the artificial gastric juice. TLC analysis indicated that four Fast Blue BB salt-positive spots were visualized (Rf values, 0.04, 0.18, 0.28, and 0.35). Rf values and the colors of two less polar spots (Rf values, 0.35 and 0.28) were identical to those of CBD and Δ^9-THC, respectively. Two other compounds (Rf values, 0.18 and 0.04) were more polar than CBD or Δ^9-THC, and a red color was developed with Fast Blue BB salt, suggesting that these compounds were the ring-cyclization products of CBD. The GC-MS analysis indicated that CBD was converted to at least four cannabinoids (peaks 1–4) (Fig. 1). Mass spectra and retention times of peak 1 and peak 2 were identical to those of Δ^9-THC and CBN, respectively (Figs. 1, 2). Peak 3 and peak 4 showed the same molecular ion at *m/z* 332 and similar fragmentation patterns (the fragment ions at *m/z* 314, 299, 271, and 231),

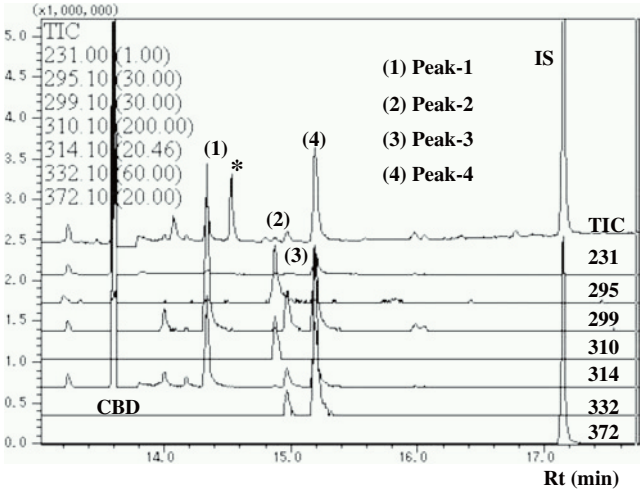

Fig. 1 Typical mass chromatograms of cannabinoids formed from cannabidiol (*CBD*) in artificial gastric juice obtained under conditions 2. *Asterisk* indicates a background peak that appeared in the control incubated without CBD

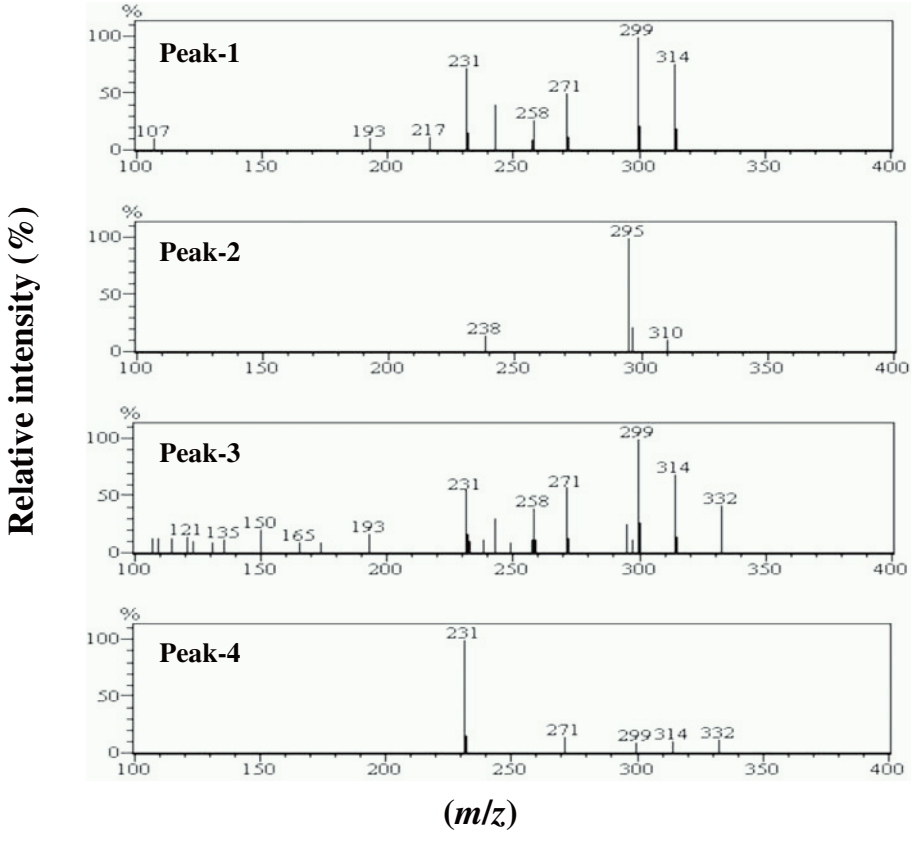

Fig. 2 Mass spectra of cannabinoids formed from CBD in artificial gastric juice, labeled as peaks 1–4 in Fig. 1

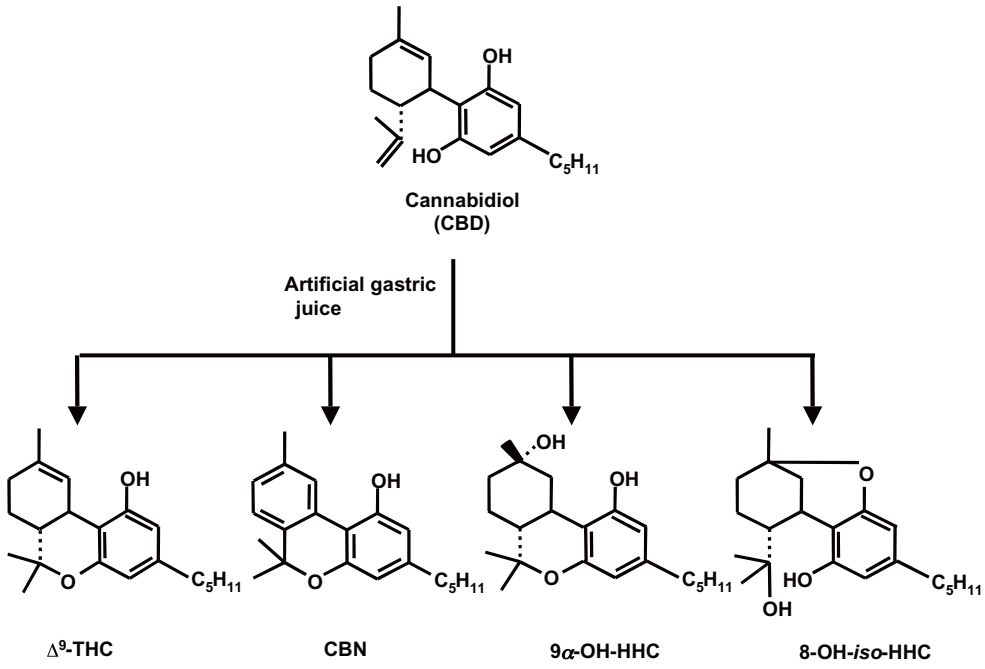

Fig. 3 Conversion of CBD to Δ^9-tetrahydrocannabinol (Δ^9-THC) and related cannabinoids in artificial gastric juice. CBN, cannabinol; 9α-OH-HHC, 9α-hydroxyhexahydrocannabinol; 8-OH-*iso*-HHC, 8-hydroxy-*iso*-hexahydrocannabinol

indicating that the molecules were larger than CBD by 18 mass units and were isomers of each other (Fig. 2).

The retention times and mass spectra of peak 3 and peak 4 were identical to those of 9α-OH-HHC and 8-OH-*iso*-HHC, respectively, prepared by the chemical syntheses described in Materials and methods. These results show that CBD can be converted to 9α-OH-HHC and 8-OH-*iso*-HHC together with Δ^9-THC and CBN in the artificial gastric juice (Fig. 3). The conversion rates for Δ^9-THC, CBN, 9α-OH-HHC, and 8-OH-*iso*-HHC from CBD were 2.9%, 1.1%, 1.4%, and 10.0%, respectively, under the conditions in the present study.

Gaoni and Mechoulam [7] reported that CBD was readily converted to Δ^9-THC and *iso*-THC in a number of acidic reagents. They also reported that treatment of CBD with sulfuric acid in methanol gave a mixture of methoxy-*iso*-HHCs and methoxy-HHCs [7], and that the boiling of CBD with diluted HCl in ethanol gave two stereoisomers of 9-ethoxy-HHCs [6].

A number of investigators have insisted that Δ^9-THC is the only psychoactive component of marijuana. Little attention has been paid to the pharmacological effects of HHCs, although some HHC derivatives were reported to have THC-like pharmacological effects [15–17]. In the present study, pharmacological effects of 9α-OH-HHC and 8-OH-*iso*-HHC have been assessed in mice by catalepsy, hypothermia, pentobarbital-induced sleep prolongation, and antinociception as indices, and have been compared with those of CBD or Δ^9-THC. 9α-OH-HHC and 8-OH-*iso*-HHC exhibited cataleptogenic effects in mice, although their activities were much lower than that of Δ^9-THC (Table 1). In the present study, the ED_{50} (mg/kg, i.v.) of Δ^9-THC was 1.9 (1.3–2.7) and comparable with the data previously reported [18]. CBD failed to induce the cataleptogenic effect at doses up to 30 mg/kg i.v. The results indicate that, for the cataleptogenic effect, both HHCs are more active than the precursor CBD, but less active than Δ^9-THC in mice.

Table 1 Cataleptogenic effects of 9α-hydroxyhexahydrocannabinol (9α-OH-HHC) and 8-hydroxy-*iso*-hexahydrocannabinol (8-OH-*iso*-HHC) in mice

Cannabinoid	ED_{50} (mg/kg, i.v.)
9α-OH-HHC	8.0 (4.0–16.2)[a]
8-OH-*iso*-HHC	30.4 (6.3–147)
Δ^9-THC	1.9 (1.3–2.7)

The bar test was carried out 15 min after the injection of cannabinoids (i.v.) by placing the front paws of the mouse on a bar. If the mouse maintained in this position for more than 30 s, the cataleptogenic effect was regarded as positive. ED_{50}, effective dose producing a 50% reduction of control; Δ^9-THC, Δ^9-tetrahydrocannabinol

[a] 95% Confidence limits shown in parentheses

Δ^9-THC is known to produce hypothermia, which is one of the typical pharmacological effects of cannabinoids in experimental animals [19–21]. In the study using CB_1 receptor knockout mice, it was shown that the hypothermic effect of Δ^9-THC was mediated through the CB_1 receptor [22]. Conflicting data were reported for the effects of CBN and CBD on the body temperature of animals, depending on the experimental conditions used

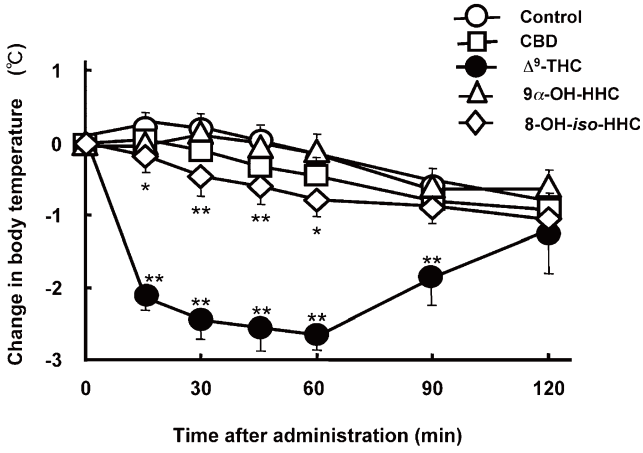

Fig. 4 Effects of intravenous administration of CBD-derived cannabinoids (10 mg/kg each) on rectal temperature of mice. The data are shown as means ± SE obtained from eight mice. *Asterisk*, significant difference from controls at $P < 0.05$; *double asterisk*, $P < 0.01$

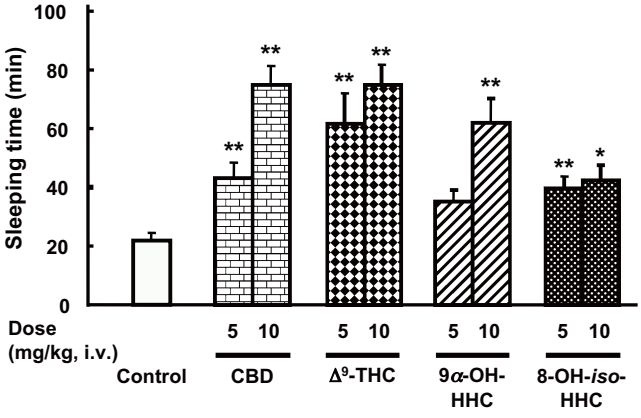

Fig. 5 Effects of intravenous administration of CBD-derived cannabinoids on pentobarbital-induced sleeping time in mice. The effects were determined under the conditions described in Materials and methods. The data are shown as means ± SE obtained from 8–24 mice. *Asterisk*, significant difference from controls at $P < 0.05$; *double asterisk*, $P < 0.01$

[23–27]. The hypothermic effects of these cannabinoids were far less potent than that of Δ^9-THC. 9α-OH-HHC and 8-OH-*iso*-HHC did not show any significant hypothermia at a dose of 5 mg/kg i.v. (data not shown), but the latter cannabinoid at the dose of 10 mg/kg i.v. exhibited a significant hypothermia from 15 to 90 min after administration with the maximum temperature difference of –0.6°C in comparison with each level of the controls. CBD (10 mg/kg, i.v.) failed to produce significant hypothermia under the same conditions (Fig. 4).

Δ^9-THC and CBD are known to potentiate barbiturate-induced sleeping time [28–30], although their mechanisms are different from each other. Δ^9-THC prolongs sleeping time by direct action on the central nervous system, possibly through the CB_1 receptor, while CBD potentiates the barbiturate effect by the inhibition of hepatic cytochrome P450 [31,32]. 8-OH-*iso*-HHC (5 mg/kg, i.v.) significantly prolonged pentobarbital-induced sleeping time by 1.8 times as compared with the control level (mean sleeping time 22.0 min) (Fig. 5). Both HHCs (10 mg/kg, i.v.) significantly prolonged pentobarbital-induced sleeping time by 1.9 to 2.8 times. However, such effects of 9α-OH-HHC and 8-OH-*iso*-HHC were much less active than those of Δ^9-THC and CBD.

In addition to catalepsy, hypothermia, and barbiturate synergism, Δ^9-THC possesses antinociceptive effects in experimental animals [13,33,34]. Although 9α-OH-HHC and 8-OH-*iso*-HHC also exhibited an antinociceptive effect against the acetic acid-induced writhing test, their effects were much weaker than those of Δ^9-THC (Table 2). CBD did not show any significant effect at 10 mg/kg i.v. in these experiments.

Table 2 Antinociceptive effects of 9α-OH-HHC and 8-OH-*iso*-HHC in mice

Cannabinoid	ED_{50} (mg/kg, i.v.)
9α-OH-HHC	14.1 (8.7–23.0)[a]
8-OH-*iso*-HHC	39.4 (6.8–226)
Δ^9-THC	1.1 (0.6–2.0)[b]

0.7% Acetic acid (10 ml/kg, i.p.) was administered 20 min after the injection of each cannabinoid or the vehicle (1% Tween 80-saline, 10 ml/kg, i.v.). The numbers of abdominal constriction were recorded for 10 min

[a] 95% Confidence limits shown in parentheses

[b] Data taken from our previous report [13]

The present study demonstrated that CBD was converted to two HHCs together with Δ^9-THC and CBN in the artificial gastric juice. Marijuana is sometimes ingested together with candies, cakes, or alcoholic drinks, and, therefore, CBD in marijuana can be converted to Δ^9-THC and HHCs under the acidic conditions in the stomach before absorption into the body, thus contributing to potentiation of the effects of Δ^9-THC originally present in marijuana.

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