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Pharmacokinetics of oral and intravenous cannabidiol and its antidepressant-like effects in chronic mild stress mouse model

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ABSTRACT

Cannabidiol (CBD) exhibits significant efficacy in mental and inflammatory diseases. Several studies have recently reported on the rapid antidepressant-like effects of CBD, suggesting that CBD is a potential anti-depressant or anti-stress drug. However, CBD is mainly administered orally or by inhalation with poor bioavailability, resulting in high costs. We aim to explore the efficacy of long-term periodic administration of CBD in chronic mild stress (CMS) via two routes and its pharmacokinetics. We treated ICR mice with CBD administered orally and intravenously and then determined the kinetic constants. A single bolus intravenous injection of CBD resulted in a half-life of 3.9 h, mean residence time of 3.3 h, and oral bioavailability of about 8.6%. The antidepressant-like effects of periodically administered CBD on the chronic mild stress mouse model are evaluated. Results demonstrated that such treatment at a high dose of 100 mg/kg CBD (p.o.) or a low dose of 10 mg/kg CBD (i.v.), elicited significant antidepressant-like behavioral effects in forced swim test, following increased mRNA expression of brain-derived neurotrophic factor (BDNF) and synaptophysin in the prefrontal cortex and the hippocampus. Our findings are expected to provide a reference for the development of intravenous antidepressant formulations of CBD.

1. Introduction

Cannabidiol (CBD), the major non-intoxicating component of cannabis (Mechoulam, 1970; Russo, 2017; Pellesi et al., 2018), varies from tetrahydrocannabinol (THC). CBD exhibits psychoactive, neuroprotective (Lastres-Becker et al., 2005; El-Remessy et al., 2006), and anti-inflammatory (Rajesh et al., 2010; De Petrocellis et al., 2011) effects and shows efficacy in neuropsychiatric disorders (Devinsky et al., 2014). These conditions include epilepsy (Carlini and Cunha, 1981; Devinsky et al., 2014; Leo et al., 2016), schizophrenia (Zuardi et al., 2006; Morgan and Curran, 2008), depression (Zanelati et al., 2010; Campos et al., 2013; Manini et al., 2015), multiple sclerosis (Rog et al., 2005; Pertwee, 2009), and neuroinflammation (Esposito et al., 2007; Mori et al., 2017). The efficacy and safety of CBD is also currently being assessed in Dravet Syndrome (Devinsky et al., 2017, 2018) and Lennox–Gastaut syndrome (Thiele et al., 2018). The frequency of seizures is significantly reduced with CBD treatment, and most adverse events, such as diarrhea, somnolence, pyrexia, decreased appetite, and vomiting, were mild or moderate. CBD has recently been approved for epilepsy therapy by Food and Drug Administration (FDA)(CBD-OS for the treatment of Lennox-Gastaut syndrome and Dravet syndrome FDA advisory committee meeting briefing document, 2019).

Depression is one of the leading causes of disability worldwide. The World Health Organization estimates (Depression, 2018) more than 300 million people currently suffering from depression, which reflects an increase of more than 18% from 2005 to 2015. Monoamine-based antidepressants comprise the first-line therapy for depression; however, their long therapeutic delays (Escande et al., 1995) and low remission rates (about 30%) (Rush et al., 2006) have prompted the search for more effective agents.

Several studies (El-Alfy et al., 2010; Zanelati et al., 2010; de Mello Schier et al., 2014; Sales et al., 2018) have reported that CBD induces

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rapid-acting antidepressant-like behavioral effects in rodents. However, these effects occur in a dose-dependent manner (Zanelati et al., 2010; Sales et al., 2018): higher dose (> 10 mg/kg, i.p.) produces significant antidepressant-like effects, whereas low-dose CBD not.

CBD may induce considerable medical effects in depression, but its bioavailability (Deiana et al., 2012; Schonhofen et al., 2018) remains a major problem in clinical trials. Medical cannabis is usually administered to patients either via inhalation (Ravula et al., 2018; Schlienz et al., 2018), spraying (Scully, 2007), or oral consumption as oil (Pellesi et al., 2018), capsules (Badowski, 2017), and cookies (Cao et al., 2016). The bioavailability of CBD considerably varies depending on the type of oral administration (p. o.): for inhaled cannabis, bioavailability largely depends on inhalation characteristics (e.g. depth, duration, breath hold), whereas oral bioavailability is determined by gastrointestinal degradation and extensive first-pass metabolism (McGilveray, 2005). The bioavailability of oral CBD ranges from 5% to 19% (Grotenhermen, 2003; Scuderi et al., 2009), and that of inhaled CBD ranges from 13% to 31% (Grotenhermen, 2003; Karschner et al., 2011).

CBD is typically administered orally or by inhalation in humans. Intravenous administration of CBD can prevent the breakdown of CBD within the gastrointestinal constants and the first-pass metabolism of the liver. The current study determines whether intravenous injection is an effective route of administration for low-dose CBD. Moreover, this study further explores whether low-dose intravenous CBD can produce effects similar to those of high-dose intravenous CBD in CMS mouse models. Accordingly, we used two routes of administration for the pharmacokinetic study: oral administration using two dosing regimens (100 and 10 mg/kg of CBD) and intravenous injection using low doses (10 mg/kg, CBD was dissolved in fat emulsion (Fortner et al., 1975; Cox et al., 1998; Hippalgaonkar et al., 2010)), and we explored the efficacy of CBD in behavioral testing and the corresponding molecular levels of mRNA in mice under different periodic dosing via different routes of administration.

2. Materials and methods

2.1. Chemicals

High-purity CBD powder (99.8%) was isolated from legal economic cannabis plants (hemp) and provided by Hanyi Biotechnology Beijing Co., Ltd, China. Soybean oil and fat emulsion purchased from Shanghai Aladdin Bio-Chem Technology Co., Ltd. (China) were used to dissolve the CBD. For the intravenous preparation, CBD was added into the lipid emulsion, vortexed for 2 min, mixed for 10 min in an air shaker, incubated at 55 °C for 1 h, and mixed for 1 h until no sticky particles were visible, a detailed assessment may require further experiments. Both for oral and intravenous administration, the concentration of CBD formulation is 3.5 mg/mL.

2.2. Animals

Specific-pathogen-free male ICR mice (35 ± 3 g, n = 60) aged 6 weeks were purchased from Weitong Lihua (licensed by Charles River, China). For pharmacokinetic study, 12 mice were used, 3 of them for each group; and for CMS program (or control), 48 mice were used, 8 of them for each group, following different treatments of CBD. The animals were housed in standard laboratory cages in the animal facility under the following conditions: controlled temperature, 22 °C ± 1 °C; humidity; 30%–70%; light/dark cycle, 6 a.m. lights on/6 p.m. lights off; and access to water and standard diet, *ad libitum*. Before the experiments were conducted, the animals were acclimatized to the animal facility for 1 week. All experiments were performed within the same period (2–6 p.m.).

Animal Ethics Committee of CAU registration No. CAU20180327-3.

2.3. Animal experiments

2.3.1. Chronic mild stress

The induction scheme of the model was based on a method used in a previous study (Willner, 1997, 2005), with several modifications. The stress program included moist bedding for 24 h, cold water immersion for 1 h, food/water deprivation for 48 h, and restraint (mice only suffering one type of stress for a period) for 1 h. The entire stressing process lasted for 4 weeks. CBD or a vehicle was given to mice weekly since the second week.

2.3.2. Forced swim test

As described in a previous study (Can et al., 2012), water about 15 cm deep (22 °C – 24 °C) was placed in a glass cylinder measuring 15 cm in diameter and 25 cm in height. The mice were subjected to a 6 min behavioral test and videotaped, and the final 4 min of the video was used for statistics. Behavioral testing of each mouse was separately conducted.

2.4. Bioanalytical methods and validations

To exclude the effects of time rhythm on drug metabolism in mice, animals were dosed between 2 and 6 p.m. The mice were treated in batches (n = 3/Group): about 20 mg/kg CBD or a vehicle treatment administered p.o. and 10 mg/kg (or vehicle treatment) administered intravenously for less than 3 min. Plasma was subsequently collected using sodium heparin-laced tubes pre-dosing and 10 min, 20 min, 40 min, 60 min, 80 min, 2 h, 4 h, 8 h, 12 h, and 24 h after dosing. The volume of the plasma at each time point was about 10–30 μL, stored at −20 °C prior to analysis. Determination of all plasma samples was conducted by WuXi AppTec Co., Ltd. (China). CBD in plasma was first precipitated with methanol and then reconstituted with acetonitrile. CBD concentration was then determined by LC-MS/MS.

2.5. Pharmacokinetic analyses

With the data of plasma concentration, we generated the concentration–time graph and linearized the data by using a semi-log graph in OriginPro 2018C (Originlab Co., Ltd., USA), with the following pharmacokinetic constants: maximum concentration of CBD (Cmax), time of maximum concentration (Tmax), area under the concentration–time curve (AUC), AUC from the time of dosing (Dosing_time) to 24 h (AUC 0–24), AUC from Dosing_time extrapolated to infinity, based on the last predicted concentration (AUC 0–inf), elimination rate constant (K), and terminal elimination half-life (t1/2) defined as 0.693/K. Mean residence time (MRT) was calculated using AUMC 0-inf /AUC 0-inf. Clearance (CL) and apparent volume of distribution (Vd), defined as CL/K.

Pharmacokinetic (PK) parameters analyzed by Phoenix Winnolin 6.0 (Certara USA, Inc., USA) included all subjects with no major deviations related to drug intake (that for each group, n = 3). In the PK analyses, the data of concentration, which value were below the limit of quantification (BQL) is 5 ng/mL, were excluded from the calculation of the PK parameters for its inaccuracy. Non-compartmental analysis of the PK parameters of CBD was summarized by the number of observations, arithmetic and geometric means, standard error, minimum of each treatment, and maximum of each treatment.

2.6. RNA extraction and real-time RT–PCR

Total RNA extraction and quantitative real-time PCR were conducted as described in a previous report (Yu et al., 2014). Data were analyzed using LightCycler® 480 ver. 1.5 (Roche, Switzerland). Relative quantification of gene expression was performed using the standard curves and normalized to the value for glyceraldehyde 3-phosphate dehydrogenase (GAPDH) in each sample. Primers for BDNF, Ionized

Table 1
Primers used in real-time PCR.

Primer name	Primer sequence (5' to 3')
GAPDH-F	AGGTCGGTGTGAACGGATTTG
GAPDH-R	TGTAGACCATGTAGTTGAGGTCA
BDNF-F	TTACCTGGATGCCGCAAACAT
BDNF-R	TGACCCACTCGCTAATACTGTC
Syp-F	CAGTTCCGGGTGGTCAAGG
Syp-R	ACTCTCCGTCTTGTTGGCAC
IBA1-F	ATCAACAAGCAATTCCTCGATGA
IBA1-R	CAGCATTCGCTTCAAGGACATA

calcium binding adaptor molecule 1 (IBA1), SYP, and GAPDH are listed in Table 1.

2.7. Statistics

All values were expressed as mean ± standard error mean unless otherwise stated. To determine statistically significant differences among the experimental groups, *t*-test or one-way ANOVA was used, followed by the Least Significant Difference. P value < 0.05 was considered significant (95% confidence interval for the difference). PASW Statistics 18.0.0 (SPSS Inc., USA) and GraphPad Prism 6.01 (GraphPad Software Inc., USA) were used.

3. Results

3.1. Pharmacokinetics of CBD in ICR mice

Fig. 1 shows the geometric mean plasma concentration–time profiles, and the semi-log graph in Fig. 2 demonstrates the metabolism and elimination of CBD. The slope of plasma concentration is biphasic,

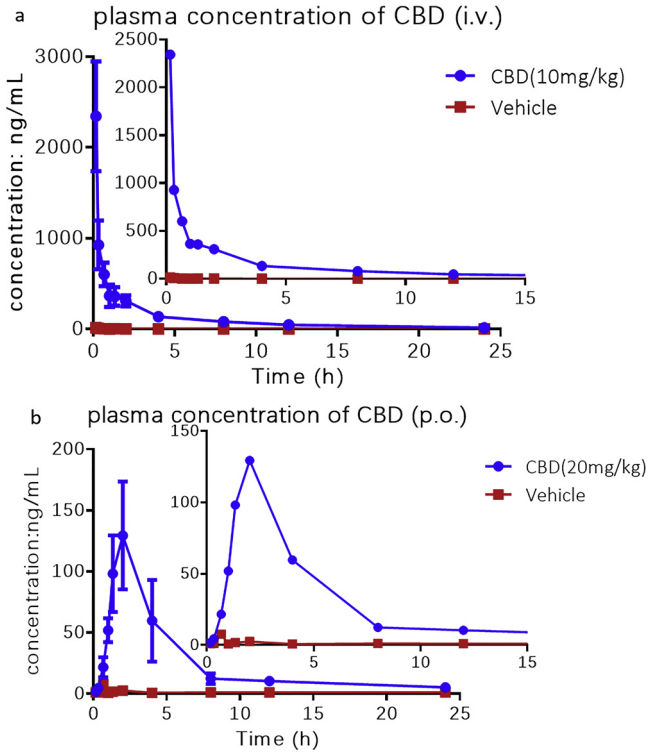

Fig. 1. Graph depicting the plasma concentration of CBD vs. time; Mean ± SEM, n = 3.
(a) Plasma concentrations of CBD vs. time with intravenous administration (10 mg/kg CBD or vehicle); (b) Plasma concentrations of orally administered CBD (20 mg/kg CBD or vehicle) vs. time.

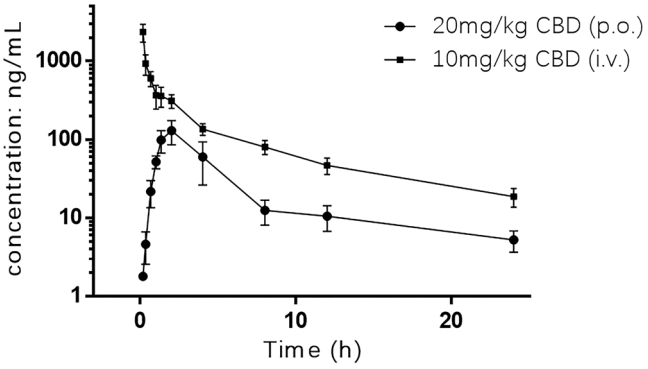

Fig. 2. Semi-log graph depicting the mean plasma concentration of orally and intravenously administered CBD vs. time.

Table 2
PK analyses of CBD.

(a) Plasma concentration of CBD via oral and intravenous administration that used for PK analyses

time	plasma concentration (ng/mL)		
	CBD (p.o., 20 mg/kg)		
10 min	–	–	–
20 min	–	–	–
40 min	9.28	18.5	37.3
1 h	36.2	49.9	69.8
80 min	41.7	103	150
2 h	52.4	131	205
4 h	20	33	126
8 h	8.01	8.12	21.2
12 h	–	–	–
24 h	–	–	–
	CBD (i.v., 10 mg/kg)		
10 min	1350	3440	2240
20 min	422	1020	1340
40 min	349	672	784
1 h	267	223	608
80 min	176	369	532
2 h	201	316	414
4 h	91.1	146	168
8 h	48.7	89.3	103
12 h	33.5	37.7	68.5
24 h	–	13.7	23.6

(b)Noncompartmental pharmacokinetic constants in orally and intravenously administered CBD. Mean (CV%), n = 3.

Parameter	Units	p.o.	i.v.
dose	mg/kg	20	10
$t_{1/2}$	h	–	3.9 (9.5)
T_{max}	h	2	0.167
C_{max}	$ng{\cdot}L^{-1}$	129.5 (58.9)	2343.3 (44.7)
$AUC_{(0-t)}$	$ng{\cdot}h\cdot L^{-1}$	551.0 (79.2)	3191.0 (38.1)
$AUMC_{(0-t)}$	$ng{\cdot}h^2{\cdot}L^{-1}$	2630.6(104.4)	11,112.8 (58.4)
$MRT_{(0-t)}$	h	4.2 (28.6)	3.3 (30.9)
CL/F	$L{\cdot}h^{-1}{\cdot}kg^{-1}$	51.2 (66.3)	3.4 (43.5)
Vd/F	$L{\cdot}kg^{-1}$	215.3 (77.2)	19.5 (47.6)
F(%,approx)		8.63%	–

which proves the presence of a distribution phase and an elimination phase in CBD. The PK parameters were then summarized using the pharmaceutical software Phoenix 6.0. Table 2(a) shows the data of plasma concentration that used for PK analyses, Table 2(b) lists the PK parameters. Compared to plasma concentration of oral CBD, the concentration of the intravenously administered drug mostly remained above BQL within the period of 24 h, that for the half-life or mean residence time (MRT), which were calculated from the data of CBD via i.v. administration could be more accurate. Oral bioavailability can be

derived from the following formula:

F = [AUC 0-inf (p.o) * Dose (i.v)] / [AUC 0-inf (i.v) * Dose (p.o)])

The bioavailability of oral CBD was 8.6%. These constants indicate that oral CBD remains in the gastrointestinal tract for an extended time and results in extremely low bioavailability owing to extensive first-pass effects. However, oral medications may exert a broad range of effects on systemic organs and tissues. On the basis of the PK data of CBD, we considered that 10% oral dosing for i.v. could exert similar effects, while certain oral dosing exhibited significant effects. Thus, in the subsequent experiment exploring the long-term effects of CBD dosage on chronic stress and depression, we used 100 mg/kg oral dose and 10 mg/kg intravenous dose (10 mg/kg p.o. for comparison).

3.2. Antidepressant-like effects of CBD

3.2.1. CBD exerts antidepressant-like effects in low-dose intravenous and high-dose oral administration

To verify whether low-dose CBD with intravenous injection can provide an efficacy equivalent to that of oral high-dose CBD, we used CMS-induced mouse models of depression and administered several drug treatments to the mice during induction. The time course for CMS and the CBD treatment is presented in Fig. 3(a). The forced swim test (FST) results in Fig. 3(b) show that both 10 mg/kg CBD (i.v.) and 100 mg/kg CBD (p.o.) significantly improved the depressive behavior in mice, whereas 10 mg/kg (p.o.) seemed to exert no effects on FST, indicating that intravenous injection of low-dose CBD markedly improved bioavailability and elicited antidepressant-like effects. Periodically administered CBDs can reverse the depression-induced symptoms of chronic stress, probably not only by their short-term neurological excitatory effects. CBD may alter the nutrient environment of brain nerve signals and strongly influence the neural function of stress-sensitive areas (the prefrontal cortex and the hippocampus). We subsequently used fluorescence quantitative techniques to detect changes in the mRNA levels of several related proteins in the hippocampus and the prefrontal cortex and further explored the mechanism by which CBD exerts sustained antidepressant-like effects.

3.2.2. CBD improves the mRNA expression of neuroplasticity-related protein in the prefrontal cortex and inhibits mRNA expression of IBA1

BDNF is an important protein that maintains the normal function of neurons and astrocytes (Shirayama et al., 2002). We first examined whether CBD alters the expression of BDNF in the hippocampus and prefrontal lobes. We found that CBD (10 mg/kg i.v. or 100 mg/kg p.o.) could increase the mRNA expression of BDNF, as shown in Fig. 3(a). In addition, chronic stress can lead to impaired synaptic function in the prefrontal cortex and the hippocampus, which is also described as the process of depression, and CBD can increase the mRNA levels of synaptophysin (SYP), which is essential for synaptic plasticity(Janz et al., 1999), to a certain extent in the prefrontal cortex and the hippocampus [Fig. 3(c)]. Recent studies have found no significant correlation between depression and neuroinflammation. Microglia act as resident immune cells in the brain, and stress causes glial cells to transform into the M1-like type, with specific high expression of IBA1(Ito et al., 1998), mediating neuroinflammation. Meanwhile, CBD can reduce the expression of IBA1 in the prefrontal cortex [(Fig. 3(b)], indicating that CBD can exert its antidepressant-like effect by inhibiting neuroinflammation.

4. Discussion

CBD exhibits significant efficacy in mental and inflammation-related diseases, but its low bioavailability via oral administration or inhalation limits its broad applications. In addition, the long-term effects of CBD on chronic stress and depression have yet to be determined. In this study, we investigated the pharmacokinetics and efficacy of CBD administered via two routes. We found that low-dose intravenous injection of CBD exhibited significant antidepressant-like activity by increasing the expression of BDNF and inhibiting microglial activation in the prefrontal cortex of mice.

Several studies have been conducted on the pharmacokinetics of CBD in mice. In the study by Deiana et al. (Deiana et al., 2012), the apparent half-life of cremophor-based CBD (p.o. and i.p.) is about 4 h. In the report by Karler et al. (Karler et al., 1979), the apparent t1/2 of CBD is only ˜1 h, Tmax is 1–2 h, and the half-life of its effects may last for 7 h with CBD injected in an alcohol solution with 3% Tween 80. Zgair et al. (Zgair et al., 2015) intravenously administered rats with a bolus of 5 mg/kg CBD (10 mg/mL) and achieved t1/2 of approximately 1.4 h. Paudel et al. (Paudel et al., 2010) obtained t1/2 of about 1 h, and CBD (polyethylene glycol formulation) absorbed intranasally within 10 min has a bioavailability of 34%–46%. Cherniakov et al. (Cherniakov et al., 2017) determined that terminal t1/2 ranges from 1.2 h to 1.7 h (in Pro NanoLipospheres), Tmax is 1 h, and bioavailability is 9%. Moreover, Brenneman et al. (Brenneman et al., 2018) reported on oral CBD [solution in propylene glycol–ethanol–sterile water (80:10:10)] with a terminal t1/2 of ˜3.5 h, Tmax of about 0.5 h, and bioavailability of 8%. These studies have indicated that the half-life of CBD is significantly affected by animal strain, background, and experimental conditions.

In the present study, noncompartmental PK analysis of CBD revealed the following: t1/2 of CBD, 3.9 h; MRT (i.v.), and 3.3. h; MRT (p.o.), 4.2 h. The mean absorption time (of oral CBD was 0.9 h, indicating that oral CBD is mostly absorbed within an hour. Clearance (CL) and Volume of distribution (Vd) were 3.4 $L{\cdot}h^{-1}kg^{-1}$ and 19.5 $L{\cdot}kg^{-1}$, respectively, and the oral pharmacokinetic data are similar. From the semi-log graph of intravenous CBD, the biphasic of the curve slope means that the absorption, distribution, metabolism, and excretion (ADME) of CBD is consistent with the two compartment model. This suggests the extensive biotransformation of CBD and wide distribution in the body. The oral bioavailability of CBD is 8.6%. CBD is a small lipophilic non-polar molecule; however, the extremely low bioavailability of CBD under extravascular administration is difficult to explain, together with the effects of fist-pass metabolism, as well as chemical or enzymatic degradation and expulsion of membrane proteins such as P-glycoprotein.

Studies have also reported (Zanelati et al., 2010; de Mello Schier et al., 2014; Linge et al., 2016; Sartim et al., 2016; Campos et al., 2017; Sales et al., 2018) that CBD exhibits antidepressant-like effects and that intraperitoneal injection of CBD can induce antidepressant-like behavioral effects within 30 min in mice. In addition, CBD may act on 5-HT1a, CB1 receptor, or the BDNF level of prefrontal cortex (Zanelati et al., 2010; Linge et al., 2016; Sales et al., 2018).

In the current study, we confirmed whether intravenous injection of CBD can induce long-term antidepressant-like effects. The findings indicate that 10 mg/kg CBD (i.v.) or 100 mg/kg CBD (p.o.) administered weekly for four weeks can significantly improve depressive symptoms, whereas 10 mg/kg CBD p.o. exerted no significant effects. Moreover, CBD increased the mRNA expression of BDNF in the prefrontal cortex. We also detected that CBD may inhibit microglial activation (as mRNA expression of IBA1 was decreased) caused by stress-induced depression (Norden and Godbout, 2013; Kreisel et al., 2014), which may affect the neurological function or neurogenesis of the prefrontal cortex and the hippocampus. The mRNA expression of SYP also increased in the prefrontal cortex and the hippocampus. This finding indicates that CBD can improve neuroplasticity, increase synaptic response, and help maintain memory and emotional status in the prefrontal cortex and the hippocampus.

In conclusion, the bioavailability of oral CBD is 8.6%, and MRT (p.o.) is 4.2 h. The t1/2 of CBD is 3.9 h, and MRT is 3.3 h. Compared with intravenous drugs, oral CBD requires almost 1 h for absorption,

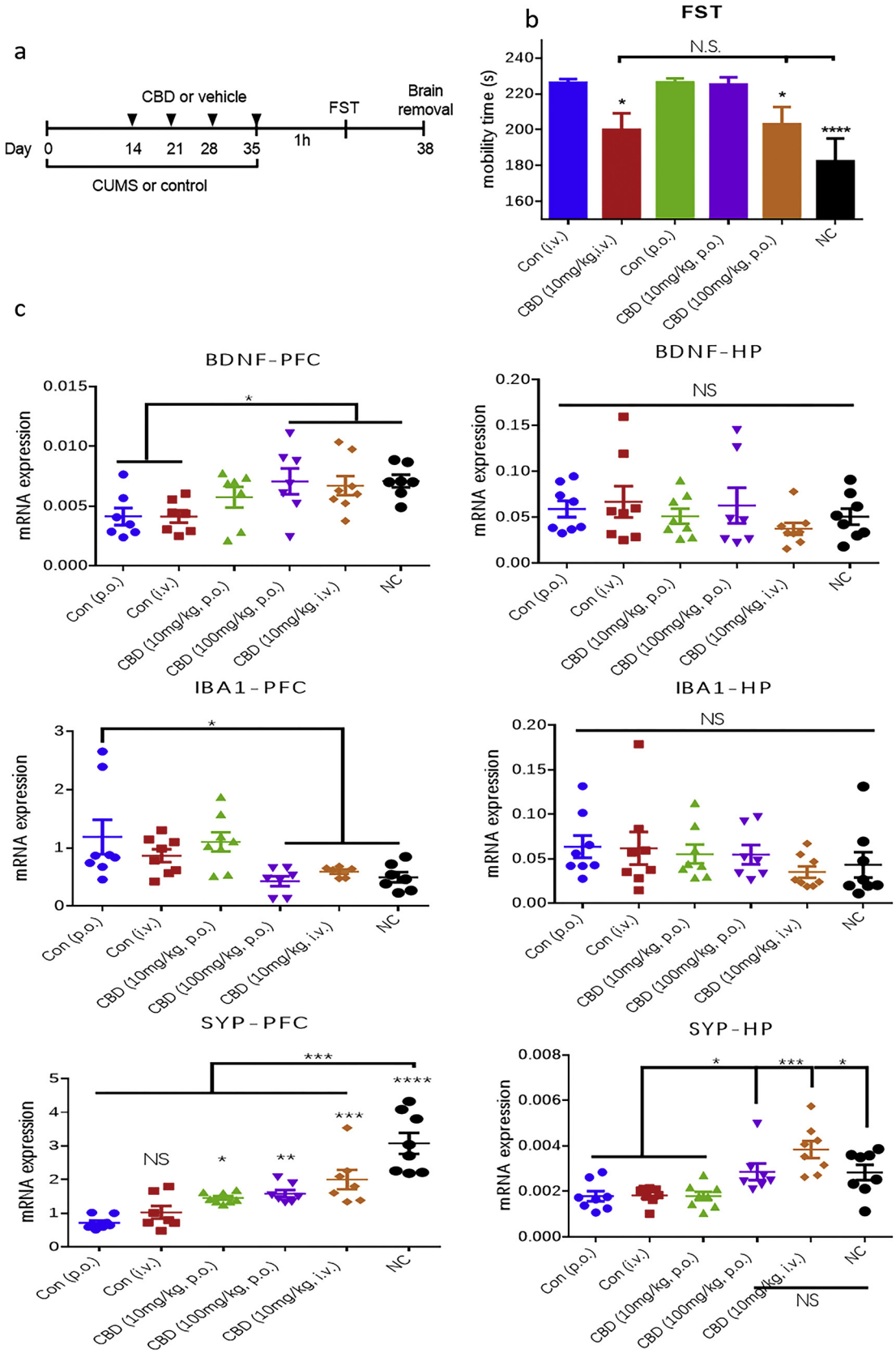

Fig. 3. Antidepressant-like effects of CBD on the CMS ICR mouse model.
(a) Time course of chronic mild stress (CMS) and treatment; (b) Forced swim test of mice after CBD or vehicle treatment. Mean ± SEM, n = 8. * means P value < 0.05; (c) The mRNA expression of BDNF, SYP, and IBA1 in the prefrontal cortex and the hippocampus. Mean ± SEM, n = 6-8. * means P < 0.05, ** means P < 0.01, *** means P < 0.001, **** means P < 0.0001.

and its extremely low bioavailability suggests that the development of an intravenous formulation would be beneficial. In addition, we found that the periodic administration of CBD exerts sustained antidepressant-like effects and improve neurological function in the prefrontal cortex and the hippocampus.

Conflict of Interest

The authors declare no conflict of interest.

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