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Prohedonic Effect of Cannabidiol in a Rat Model of Depression

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Key Words
Cannabidiol · Wistar-Kyoto rats · Anhedonia · Depression · Anxiety

Abstract
Background: Accumulating evidence suggests that cannabidiol (CBD) may be an effective and safe anxiolytic agent and potentially also an antidepressant. ***Aim:*** The objective of this study was to further examine these properties of CBD using the 'depressive-like' Wistar-Kyoto (WKY) rat, focusing on the drug's effect on anhedonia-like behaviors. ***Methods:*** Forty-eight WKY and 48 control Wistar adult male rats were pretreated orally with CBD (15, 30 and 45 mg/kg) or vehicle. The saccharin preference test (SPT), the elevated plus maze (EPM) test and the novel object exploration (NOE) test were used. ***Results:*** CBD showed a prohedonic effect on the WKY rats at 30 mg/kg in the SPT. In the NOE, CBD increased exploration of the novel object and locomotion at 45 mg/kg and increased locomotion at 15 mg/kg, indicating an improvement in the characteristically low motivation of WKY rats to explore. There was no similar effect at any dose in the EPM or in open-field behavior in the habituation to the NOE. ***Conclusions:*** These findings extend the limited knowledge on the antidepressant effect of CBD, now shown for the first time in a genetic animal model of depression. These results suggest that CBD may be beneficial for the treatment of clinical depression and other states with prominent anhedonia.

Introduction

Cannabidiol (CBD) is the major nonpsychomimetic phytocannabinoid compound present in the plant *Cannabis sativa*. Cannabis plants may contain up to 40% CBD. CBD has been shown to counteract several of the effects of Δ9-tetrahydrocannabinol, the main component of cannabis. The independent anxiolytic activity of CBD was first demonstrated within a limited range of doses in male Wistar rats, by measuring the entry ratio to open/total arms of an elevated plus maze (EPM) [1]. Later studies, also in male Wistar rats, reinforced the hypothesis that CBD (given in a single dose) is anxiolytic, using the Vogel conflict test [2], a model of contextual conditioned

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fear [3] and stress-induced behavior in the EPM [4]. Similar anxiolytic effects of CBD were demonstrated in mice subjected to chronic unpredictable stress, receiving CBD following each daily stressor [5]; however, when CBD was administered repeatedly (14 daily injections) to Lister-hooded rats [6] anxiogenic effects were found. Taken together, these data support testing the hypothesis that CBD may be used to treat anxiety in humans. Preliminary reports in humans supported this hypothesis, suggesting anxiolytic effects of CBD in patients [7]. Recently, it was shown that CBD was effective in reducing public speaking anxiety in the context of social phobia [8].

Accumulating evidence further suggested that the endocannabinoid system is involved in the pathophysiology of depression [9]. In accordance, a recent study in male Swiss mice showed that CBD induced an antidepressant-like effect in the forced swim test (FST) comparable to that of imipramine [10]. Another study in Swiss Webster mice demonstrated dose-dependent antidepressant activity in the FST; however, this effect was not extended to a tail suspension test [11]. To further validate the therapeutic potential of CBD, the effects on genetic animal models of depression/anxiety are of interest.

The Wistar-Kyoto (WKY) rat, inbred from the Wistar strain, is stress sensitive or 'depressive-like'. This strain has been established as a valid 'genetic' animal model of depression [12, 13]. Adult WKY rats demonstrated depression-like physiological symptoms such as reduced body weight and disturbed REM sleep [14], as well as 'behavioral despair' and 'anhedonia', two important criteria for the diagnosis of depression. These depression-like behavioral symptoms are demonstrated by increased immobility duration in the FST (a test of behavioral despair or alternatively a test sensitive to antidepressants [15]) and less consumption of a sweet solution in response to chronic mild and acute stress [12, 13].

WKY rats also presented anxiety-like behavior over several different behavioral tests [13, 16, 17]. We have previously reported that as early as age 30–40 days, WKY rats displayed many behavioral and physiological characteristics resembling depression and anxiety [12]. In addition, the WKY model has abnormalities in the endocannabinoid system, including lower levels of anandamide in the frontal cortex and hippocampus, compared to the Wistar strain [9], dysfunction in the CB1 receptor and fatty acid amide hydrolase [18], as well as differences in mRNA expression of several components of the endocannabinoid system in response to stress, compared to Sprague-Dawley rats [19].

The low activity of the WKY rats and their reduced exploration in novel environments imply high anxiety/depressive-like symptoms [12, 20], making them a viable model for studying the potential of CBD to mitigate the development of these pathologies.

We aimed to further study the antidepressant and anxiolytic properties of CBD using the WKY model. We assumed that CBD would decrease depressive- and anxiety-like behaviors in WKY rats compared to Wistar controls. In this report we focus on the effects of CBD on anhedonia-like behavior as demonstrated by the saccharin preference test (SPT), a popular version of the standard test of anhedonia in rodents [21]. In addition, we examined anxiety-like behaviors, using the EPM. Motivation to explore novel conditions was further examined using the novel object exploration (NOE) test. Reduced interest in a novel object may represent anhedonia and/or anxiety. Our design provides the possibility of testing for differences between anxiolytic and antidepressant effects. Another novel aspect of this study is the testing of potential effects of CBD both in a genetic model of depression and in stress-induced anhedonia.

Methods

Subjects

The study included 55 Wistar (control strain) and 51 WKY 90-day-old male rats, weighing 200–250 g. The rats were housed in polypropylene cages (38 × 21 × 18 cm, 2 per cage) in a temperature-controlled specific pathogen-free facility (22 ± 1°C) under standard laboratory conditions, with free access to standard food (2018SCF; Teklad Global 6% Fat Rodent Diet; Harlan, Madison, Wis., USA) and water and a 12-hour light/dark cycle (lights on at 07:00 h). During SPT at baseline and on the experimental day, the rats were housed in individual cages.

The rats were provided by Bar-Ilan University's colony. The study protocol was approved by the Institutional Animal Care and Use Committee and adheres to the guidelines of the Society for Neuroscience.

Chemicals

CBD was extracted from cannabis as previously described [22]. It was a crystalline product, with a melting point of 66–67°, and was above 99% pure, on the basis of mass spectral analysis.

The rats were pretreated orally with CBD (15, 30 and 45 mg/kg) or vehicle (100 μl ethanol) laced into high-fat diet pellet (rodent diet with 60% fat; D12492; Research Diets, Inc., New Brunswick, N.J., USA; n = 12 ± 2 per strain and dose).

In order to prevent neophobia, a high-fat diet pellet with a 100-μl drop of ethanol was given 4 times a week to the rats prior to the experiment (individually in a holding cage). CBD and vehicle solutions were prepared immediately before use. On the test day, each animal was placed in its holding cage and given the pellet. The rats completed eating the pellet within 5 min. The 2-hour in-

terval until testing started only after the entire pellet was consumed. Two subjects did not consume the entire pellet and were removed from the study.

Saccharin Preference Test

Individual baseline levels of saccharin preference were measured twice, on days 3 and 2 prior to the test day. The first day was regarded as habituation, and the data from the second day were used for determining baseline levels. During the baseline and test days each rat received a bottle of saccharin (0.025%) and a bottle of tap water. The total consumption of water and saccharin was measured between 13:00 h and 09:00 h. Preference ratio: (consumed saccharin ×100)/(consumed water + consumed saccharin). On the test day, the rats underwent handling and 20 min of behavioral tests (EPM and NOE, described below) before the SPT. Thus, the SPT can be considered as a test of stress-induced anhedonia.

Elevated Plus Maze

The elevated plus maze was constructed from black opaque Perspex and consisted of two open arms, 50 × 10 cm, and two enclosed arms, 50 × 10 × 40 cm with an open roof, raised 70 cm above the floor [23]. The rat was placed in the center of the plus maze facing one of the open arms and allowed to explore the maze freely for 5 min. Arm entry is defined as entering an arm with all four paws. Measures [23] for analysis included duration in the open and closed arms and number of visits to the open arm. The test was performed between 11:00 and 13:00 h.

Novel Object Exploration

This protocol was modified from Goodwin and Yacko [24] to obtain a test of unconditioned preference for a novel versus a familiar object. This could provide a measure of relative neophobia versus approach behavior. All the rats were habituated to a familiar object (stone/screw randomized) 20 h before the test. On the test day, each rat was placed in an open-field arena built from black Polygal (62 × 62 cm, with 30 cm high walls) in an illuminated room for 5 min and the locomotor activity was recorded. Next, they were removed and placed in a holding cage for ~60 s while the familiar and novel objects were placed in opposite corners of the arena (objects and positions were counterbalanced). The rats were allowed to explore the arena for an additional 5 min. The time spent near the objects, the number of contacts with the objects and locomotion (lines crossed) were measured. The test was performed between 11:00 and 13:00 h.

Behavior in the EPM and NOE was recorded with a web camera (Microsoft Life-cam VX 1,000). Digital recordings were analyzed using the public domain 'EthoLog' program. The locomotor behavior during the habituation phase of the NOE was analyzed with Ethovision (Noldus, The Netherlands).

Procedure and Design

A week prior to testing, all the rats were handled and on days 3 and 2 prior to the test SPTs were performed. On the test day, the rats were separated into holding cages, where they consumed the pellet containing CBD or vehicle. After 2 h they underwent the EPM and NOE tests (11:00–13:00 h; n = 13–16 per group in the Wistar and n = 11–14 per group in the WKY). Individual posttesting stress saccharin preference was then measured over 20 h of consumption (due to bottle leakage, n = 39, 9–11 per group in the Wistar and n = 43, 10–12 per group in the WKY).

Table 1. Comparison of behavioral patterns between WKY and Wistar rats with different doses of CBD in the EPM and NOE tests

Variable	CBD dose, mg/kg	Wistar	WKY
EPM	0	100.20±11.69	45.54±13.20[c]
Duration in the	15	100.75±9.93	46.28±8.06[c]
open arms, s	30	67.65±8.11	40.06±9.64
	45	104.75±13.64	29.28±5.85[c]
EPM	0	146.60±14.52	167.76±23.17
Duration in the	15	131.46±11.80	185.78±12.69[a]
closed arms, s	30	163.44±12.45	178.71±17.82
	45	135.78±15.06	217.92±12.50[c]
EPM	0	5.69±0.63	2.70±0.34[b]
Entries into the	15	5.54±0.55	3.36±0.46[b]
open arm, n	30	4.77±0.56	2.27±0.36[b]
	45	5.23±0.71	2.08±0.34[c]
NOE	0	3.3571±0.5	1.4000±0.65[a]
Contacts with	15	2.7000±0.7	3.6667±0.78
novel object, n	30	3.9000±1.1	3.2222±0.68
	45	2.9091±0.69	5.6667±1.41[d]

Values are means ± SD. WKY rats displayed a different behavioral pattern than the Wistar rats. [a] $p < 0.05$, [b] $p < 0.01$, [c] $p < 0.001$, for comparisons with Wistar rats. CBD significantly changed the behavior within the rat strain. [d] $p < 0.05$, for comparisons with vehicle group.

Statistical Analysis

All data were tested for normality and homogeneity of variance. The results were analyzed using multi- and univariate analysis of variance (ANOVA). For baseline-poststress comparisons of saccharin preference (only), one-factor repeated measures analysis with strain (WKY and Wistar) as independent factor and time (baseline/test day) as repeated-measures factor was employed. Duncan's test and tests for simple effects with Bonferroni adjustment were used for post hoc comparisons when relevant, with a significance level of 0.05. All tests were two-tailed. Statistical analyses were performed with SPSS 20.0 software (IBM Corp., Armonk, N.Y., USA).

Results

Elevated Plus Maze

The WKY rats showed their phenotypical anxiety-like behavioral profile on the EPM shorter duration in the open arms ($F_{1, 98} = 49.581$, $p < 0.001$), longer duration in the closed arms ($F_{1, 98} = 15.265$, $p < 0.001$) and less entries into the open arms ($F_{1, 98} = 51.941$, $p < 0.001$) compared to Wistar. However, there were no significant CBD main effects of dose or dose × strain interactions (table 1).

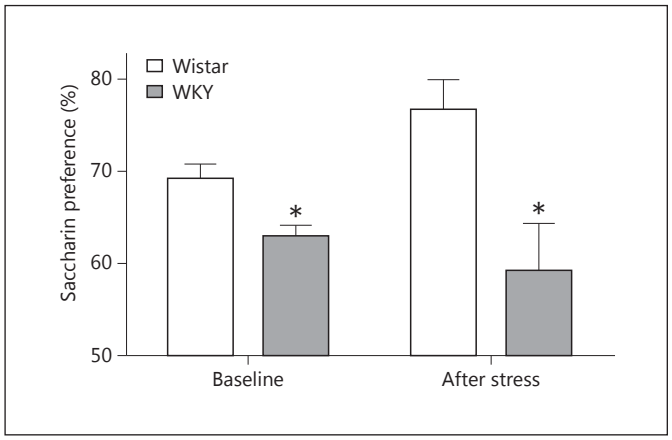

Fig. 1. In the SPT, WKY rats preferred the saccharin solution significantly less than Wistar controls at baseline (n = 43 and 42, respectively), as well as after stress testing (n = 11 and 10, respectively, vehicle groups only). In these vehicle-treated rats, there was a significant strain × test interaction showing different poststress trends in the 2 strains: WKY rats reduced saccharin preference after stress while Wistar controls appeared to increase preference after stress. * $p < 0.05$.

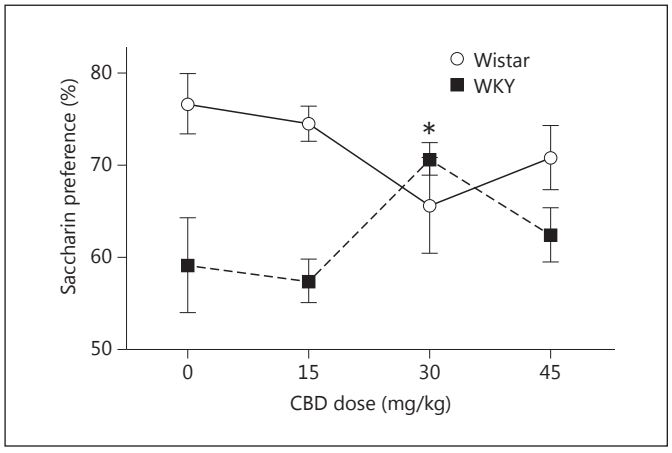

Fig. 2. In the SPT, CBD had a positive effect in normalizing saccharin preference at 30 mg/kg in WKY rats (significant dose × strain interaction). * $p < 0.05$, for the comparison of 30 vs. 0 mg/kg in WKY rats.

Saccharin Preference Test

As shown in figure 1, the WKY rats showed their phenotypical anhedonia-like reduced preference for saccharin compared to Wistar rats at baseline ($F_{1, 83} = 10.50$, $p < 0.01$) as well as after testing stress (vehicle groups, $F_{1, 19} = 7.79$, $p < 0.05$). Repeated-measures ANOVA in the vehicle groups showed a significant strain × test interaction ($F_{1, 18} = 6.37$, $p < 0.05$), supporting the trend of WKY rats to reduce saccharin preference after stress compared to Wistar controls who appeared to increase preference after stress (n = 11 and 10, respectively).

Two-way ANOVA on saccharin preference on the test day revealed a significant interaction ($F_{3, 75} = 4.22$, $p < 0.01$) and also a strain difference ($F_{1, 75} = 16.05$, $p < 0.001$; fig. 2). Duncan's post hoc analysis within strains further showed that in WKY rats, at a dosage of 30 mg/kg, saccharin preference was significantly ($p < 0.05$) higher than vehicle. In Wistar rats, the reduction in preference at 30 mg/kg did not reach significance.

Novel Object Exploration

Analysis of locomotor behavior in the habituation phase (open-field behavior) did not reveal significant differences between vehicle- and CBD-treated rats.

Two-way initial multivariate ANOVA on anxiety-like behaviors in the NOE test examined three dependent variables: time spent in seconds near the novel object, number of times contacting the novel object and locomotion – number of lines crossed. A significant interaction ($F_{9, 175.38} = 3.95$, $p < 0.001$) was found as well as a dose effect ($F_{9, 175.38} = 2.21$, $p = 0.05$).

Tests for simple effects with Bonferroni adjustment indicated that there were differences between the strains in the vehicle group for all three parameters measured: time with novel object (fig. 3a), contact with novel object (table 1) and locomotion (fig. 3b). In addition, when treated with CBD at the dosage of 45 mg/kg, the WKY rats spent significantly ($p = 0.026$) more time near the novel object than the vehicle group. Additionally, at a dosage of 30 mg/kg there was a nonsignificant tendency ($p = 0.072$) for spending more time near the novel object compared to vehicle. Moreover, the dosage of 45 mg/kg was also effective in increasing significantly ($p = 0.004$) the number of novel object contacts compared to vehicle. In both dosages (45 and 15 mg/kg), the WKY rats showed significantly ($p < 0.001$, $p < 0.007$) more locomotion than the vehicle group. For means see table 1.

Discussion

In this study we have shown that CBD had a prohedonic effect on depressive-like WKY rats at 30 mg/kg as demonstrated by the SPT. Results of the NOE demonstrate increased exploration of the novel object and locomotion at 45 mg/kg and increased locomotion at 15 mg/kg, indicating an improvement in the characteristically

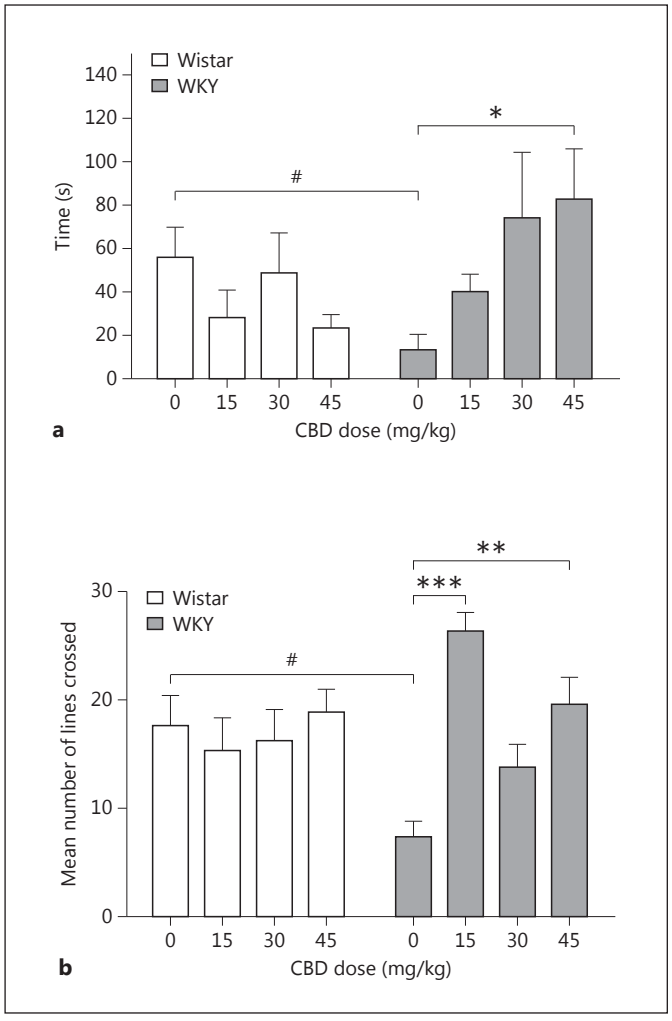

Fig. 3. In the NOE test, CBD increased the duration of contact with a novel object at the dose of 45 mg/kg (**a**) and increased locomotion at 15 and 45 mg/kg (**b**) in WKY but not in Wistar rats. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, for comparisons with vehicle group; # $p < 0.05$ for comparison with Wistar.

low motivation to explore of WKY rats. In contrast, there was no similar drug effect at any dose in the EPM or in the habituation phase of the NOE.

These findings extend the very limited knowledge on the antidepressant effect of CBD, now shown for the first time in adult WKY rats. To date, only two studies investigated the antidepressant properties of CBD, both in mice, using the FST [10, 11], thus representing only a single dimension of depression. Moreover, since a tail suspension test yielded negative findings [11], there was clearly a need for further tests to substantiate this possible antidepressant drug effect. Thus, anhedonia, a major dimension of clinical depression, was investigated in this study by different tests.

The SPT, a classic test for anhedonia in rodents (with minimal impact of locomotor abilities), suggested a prohedonic effect of CBD at 30 mg/kg by normalizing saccharin/water ratio consumption. Note that at this dose, CBD did not affect locomotion. We also attempted to extend this finding using the NOE test, representing neophobia versus curiosity/exploration (variables closely related to anhedonia versus hedonia), which yielded mostly consistent results. Whereas only a trend existed for 30 mg/kg, a significant beneficial effect was observed for 45 mg/kg. Following our negative findings in the EPM, and the increased locomotion, we suggest that in our model the effect of CBD was more antidepressant-like than anxiolytic, and therefore the positive effect in the NOE test may be attributed to increased hedonia, in line with the SPT findings. These results remain to be replicated in future studies, possibly using other methods to evaluate the effect of the drug on anhedonia.

Our focus on ameliorating anhedonia is consistent with the research strategy of the National Institute of Mental Health (NIMH) implemented by the Research Domain Criteria (RDoC) project [25]. This attempt aims at studying behavioral dimensions independently from the clinical classification systems whose validity is questioned. Investigating pharmacological strategies to improve anhedonia rather than depression may, therefore, be more accurate and might also prove beneficial for clinical states of prominent anhedonia without depression, such as borderline personality disorder and schizophrenia [26]. Patients with this prevalent lifelong disorder experience disabling emptiness and anhedonia unrelated necessarily to depression, and there are currently no available pharmacotherapies to target them. In schizophrenia, anhedonia has a key role in pathology as one of the debilitating negative symptoms.

Reports in the previous literature regarding the effective dose of CBD varied widely. Thus, different dosages were administered in our experiment. The effective dose per weight in our study was similar to that reported by Zanelati et al. [10]. However, they administered CBD intraperitoneally to the mice, and not orally to rats as in the present study. In rats, oral CBD has been shown to reach higher levels in the brain and for a longer duration compared to intraperitoneal CBD, whereas in mice the opposite pattern was reported [27], so that it is likely that more functional CBD reached the relevant receptors in our study. Interestingly, the effective dose of CBD in WKY rats in our study varied by behavioral measure. This may

reflect underlying individual differences in the optimal dose required for specific behavioral modification.

The results of this study should be interpreted in light of its limitations. First, only a single model for depression was used. Second, due to bottle leakage, we excluded data from 8 WKY rats and 16 Wistar rats, with an evident effect on the statistical power. Third, all behavioral tests were performed on the same day, while the CBD treatment was effective. In principle, one behavioral test could have influenced the behavior in the subsequent tests (in fact, we wanted the SPT to follow the other tests, as described above). Nevertheless, future studies with intertest intervals of a few days and counterbalancing could further advance our understanding of the effects of CBD (including whether repeated administration produces habituation or sensitization). Finally, the extent of generalizability of these findings in an animal model to humans is yet to be determined.

In conclusion, the results of this study suggest that CBD may be used as a pharmacological therapy for anhedonia and clinical depression. The present study is the first to use the WKY rat model of depression and to report a prohedonic effect of CBD in two different tests. As CBD was shown to be exceptionally well tolerated by humans in previous studies on anxiety disorders [7, 8] and schizophrenia [28], even in high doses, it seems a promising candidate for the future psychopharmacotherapeutic arsenal.

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Disclosure Statement

The authors have no conflicts of interest to declare.

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