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Brief communication

Effects of cannabidiol in males and females in two different rat models of depression

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ABSTRACT

The current study explores the therapeutic potential of Cannabidiol (CBD), a compound in the Cannabis plant, using both sexes of 2 “depressive-like” genetic models, Wistar Kyoto (WKY) and Flinders Sensitive Line (FSL) rats. Rats ingested CBD (30 mg/kg) orally. In the saccharin preference test, following a previous report of a pro-hedonic effect of CBD in male WKY, we now found similar results in female WKY. CBD also decreased immobility in the forced swim test in males (both strains) and in female WKY. These findings suggest a role for CBD in treating mental disorders with prominent symptoms of helplessness and anhedonia.

Major depressive disorder (MDD) is a significant cause of incapacity in the Western world. Various anti-depressant drugs are used in attempts to relieve the debilitating symptoms [26]. Although these drugs ease symptoms in about 60–70% of cases, there are numerous patients who do not find relief and the rate of remission is low [10,30]. Furthermore, a large portion of those who are responsive suffer from negative side effects such as dry mouth, abdominal pain, sexual dysfunction, increased anxiety, expressions of violence and even suicide [5]. The main target of drugs currently in use to treat MDD is monoamine neurotransmission. Over 40 years of research into the role of serotonin, a monoamine, has not resulted in the development of a universally effective treatment or a cure for the disorder. Consequently, there is great need for new pharmacological approaches both for treatment of the non-responders, and to alleviate the wide-range of adverse effects of the existing therapeutics.

The endocannabinoid system (ECS) may be a target for new anti-depressant drugs. The ECS is important for daily regulation of many basic functions such as cognition, perception, sleep, pain, appetite, reward, as well as endocrine, cardiovascular and immune responses [6,7,31]. There is increasing evidence supporting the role of the ECS in the neurobiology of depression [24,42,43]. Specifically, the ECS system can regulate hypothalamic-pituitary-adrenal (HPA) axis activity and it plays a role in both the pathophysiology and treatment of MDD [11,14–16,44]. Considering the potential of the ECS as a pharmacological target, the recent increased usage of medical marijuana, typically produced from Cannabis flowers or Cannabis plant resin extract, is not surprising [4].

Although there is therapeutic potential in cannabis, there are drawbacks as well. There are several compounds with different activities in cannabis and its activity depends on the quantity and ratio of these constituents. The psychoactive Δ9 - tetrahydrocannabinol (THC), a major constituent, causes most of the marijuana effects (the ‘high’), but is also associated with adverse side effects such as anxiety, cholinergic deficits and immunosuppression [37]. A recent publication has shown that THC treatment of adolescent male mice leads to long-term cognitive and behavioral dysfunction [25].

By contrast, cannabidiol (CBD), which is also an abundant constituent, causes anti-anxiety, anti-schizophrenia and anti-inflammatory effects [17]. It also appears to block the above-mentioned long-term cognitive and behavioral dysfunctions [25]. Despite these positive effects, there is a serious lack of carefully controlled clinical research in the field. In pre-clinical research, CBD has been found to have

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protective properties in several animal models of neurodegeneration as well as therapeutic-like effects in models of psychiatric disorders [19,29,35,46,47]. Clinical trials have indicated potential benefits in the management of Alzheimer's disease, multiple sclerosis (MS), Parkinson's disease and amyotrophic lateral sclerosis [18]. In accordance, recent evidence from our lab showed that CBD had pro-hedonic effects in male Wistar Kyoto (WKY) rats, a genetic model of depression. This effect was manifested in increased consumption of a sweet solution in the Saccharin Preference Test (SPT) and increased exploration of a novel object and locomotion in the Novel Object Exploration Test (NOE) [41].

In line with the behavioral data demonstrating antidepressant-like effects, one proposed mechanism of action of CBD is through 5-HT1A receptors [2,12,34,38,45]. These receptors modulate responses to stressful stimuli and are proposed to mediate the effects of antidepressant drugs [3,22]. However, CBD has a wide range of pharmacological actions with several suggested mechanisms, though the precise mechanisms which underlie its therapeutic effects are still unclear. Taken together, CBD has a polypharmacological profile, resulting in multiple mechanisms of action possibly responsible for its high therapeutic potential. Some of these may be involved in alleviating psychopathologies such as MDD.

The aim of the current study was to expand the translational evidence we have collected thus far and further examine CBD as a potential anti-depressant agent at a dosage of 30 mg/kg, consumed with food [41]. In our previous report, we showed the compound's potential to relieve anhedonia-like symptoms in a genetic rat model. An additional key symptom in depression is hopelessness/helplessness, often modeled in rodents by examining passive coping strategies using the forced swim test (FST). Examining CBD's ability to reduce helplessness-like behavior in addition to anhedonia will expand our understanding of its clinical potential. Recent studies have indeed shown that CBD exerts antidepressant-like effects in the FST in male mice and rats, at least partially through serotonergic pathways ([9,39,40]). Another way to examine its potential therapeutic significance would be to examine its effect on female as well as male rats, as MDD is more prevalent in women than in men [26]. Importantly, for convergent validity, the present study investigated the influence of CBD on an additional genetic rat model of depression, the Flinders Sensitive line (FSL). Both WKY and the FSL rat models present many behavioral and physiological endophenotypes that are often present in MDD making them valuable models for studying depression (for reviews see [23,27]). The present study examined the effects of acute oral self-administration of 30 mg/kg of CBD on males and females of two genetic rat models of depression, using both the SPT to assess anhedonia-like behavior and the FST for despair-like behavior. The oral route was chosen as it is the preferred translational option for potential use in humans. The study included Wistar, FSL and WKY adult male and female rats approximately 70-days-old. The rats were provided by Bar-Ilan University's colony, FSL progenitors were provided by Prof. Overstreet (FSL) and WKY progenitors were purchased from Envigo. Rats were housed in polycarbonate cages (38 × 21 × 18 cm), 2 per cage, in a temperature controlled facility (22 + 1 °C), under 12 h–12 h light:dark cycle (lights on at 07:00). Food and water were available ad libitum and a plastic tube was in the cage for enrichment. The study protocol adheres to the National Institutes of Health guide for the care and use of Laboratory animals (NIH Publications No. 8023, revised 1978) and the ARRIVE guidelines and it was approved by the Institutional Animal Care and Use Committee (protocol #46-05-2017).

The FST was as described by Porsolt et al. [32] with modifications. A Plexiglas cylinder 45.5 cm tall, 20 cm diameter was filled to 30 cm with 24 ± 0.5 °C water. The animals were immersed in the Plexiglas cylinder for 5 min.

The following measurements were recorded: immobility and struggling durations were measured online using a stop watch. The criterion for immobility was making only the minimal movements necessary to keep the head above water. The criterion for struggling was making active forepaw movements in and out of the water including climbing. Swimming was defined as activity that is not immobility or struggling and was calculated by subtracting total immobility + total struggling from the total test time. At completion of the test, animals were dried off with a towel. The cylinder was cleaned and water changed between test animals.

The SPT procedure was similar to that described in Shoval et al. [41] with modifications. Saccharin (2,3 dihydro-3-oxonenzisosulfonazole purchased from Sigma) dissolved with tap water was used in a 2-bottle test (vs. water) to assess relative preference.

Two days prior to the test day, animals were habituated to the SPT conditions by placing them individually in test cages overnight with both saccharin and water bottles in the same configuration as they would be on the test day. The habituation procedure provided baseline measures and aimed to reduce general levels of anxiety and neophobia to the saccharin solution. The animals were not deprived of water or food at any point. On the test day, 2 h after ingesting the CBD or vehicle and after exposure to the FST, each animal was presented with 2 identical bottles (200 ml), one with saccharin (0.025%) and one with drinking water. The animals had the opportunity to drink as much as they wanted during the ensuing 18 h. The bottles were weighed before and after the experiment. Bottles and nipples were checked for leakage prior to the test.

The total consumption of water and saccharin in grams was measured and was used to calculate the preference ratio as followed:

(100×saccharin consumption)/(saccharin consumption + water consumption)

In order to prevent neophobia, a high-fat diet pellet with a 70-µl drop of ethanol was given 2 times during the week 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, between 0900 and 1100 h (The rats completed eating the pellet within 5 min.). Either 30 mg/kg of CBD dissolved in 70 µl ethanol or 70 µl of ethanol (vehicle) was laced onto this pellet of high fat rodent diet (D12492 Research Diets, Inc. Rodent diet with 60% Fat, NJ USA). The consistency of the pellets differs from standard rodent chow, they are soft, allowing for the entire amount to be absorbed fully into the pellet. The animals consumed the pellet without any need of coercion. Behavioral testing began between 11:00–13:00 h, in a dedicated experimental room, 2 h after the pellet was consumed (the same time frame in which we found anti-depressive-like effects of CBD and its variant CBDA-ME [13,41]).

Two researchers performed each of the experiments. One prepared the drug solutions and was therefore not “blind” to the group assignment of the rats. The other was totally “blind”. Both researchers observed all rats together, counterbalancing the roles in scoring immobility or struggling between animals.

Experiment 1: Twenty-five male Wistar (mean weight: 250-350 g) and 30 male WKY (mean weight: 200-250 g) were pretreated with either 30 mg/kg of CBD or vehicle. Two hours after consumption of the pellet they were exposed to the FST.

Experiment 2: Twenty-one WKY female rats (mean weight: 190-250 g) consumed a pellet laced with CBD or vehicle solution (as described above) on the experiment day. Two hours later, an FST was conducted, to examine helplessness-like behavior. The rats were then placed in their individual test cages to examine anhedonia-like behavior overnigsht in the SPT.

Experiment 3: The same procedure as in Experiment 2 was conducted with 24 FSL female rats (mean weight: 200–250 g).

Experiment 4: The same procedure as in Experiment 2 was conducted with 34 FSL male rats (mean weight: 300–400 g).

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Table 1
Saccharin preference (mean ± SEM) of female Wistar Kyoto (WKY) and male and female Flinders Sensitive Line (FSL) (n = 10–15 in each group).

	Vehicle	30 mg/kg CBD
WKY Females	73.3 (2.3)	82.3 (2.3)**
FSL Males	87.8 (1.8)	89.6 (1.2)
FSL Females	82.7 (6.2)	89.6 (0.9)

** $p < 0.05$.

Between-group comparisons were performed by Student's *t*-test (for 2 group comparisons), and two-way multivariate or univariate analysis of variance (MANOVA) followed up by one-way ANOVAs with tests for simple main effects with Bonferroni adjustment on each dependent variable (where appropriate). On the FST, two measures were assessed with MANOVA: Immobility and swimming. Struggling was not included in these analyses to allow degrees of freedom.

Results of the SPT in WKY females showed, as expected, that baseline saccharin preference between control and treatment groups were not significantly different using an independent-samples *t*-test. However, an independent-samples t-test between the two treatment conditions on the test day revealed significantly higher saccharin preference for the group treated with CBD compared to vehicle treated controls (t [15] = 2.58, $p = 0.021$). (Vehicle: M = 73.3, SD = 6.06, N = 8; 30 mg/kg CBD: M = 82.3, SD = 8.09, N = 9) (Table 1).

For FSL females there was no significant baseline difference in preference between control and treatment using an independent-samples *t*-test. An independent-samples t-test on the test day did not show significant differences between the two treatment conditions. (Vehicle: M = 82.07, SD = 19.9, N = 13; CBD: M = 90.68, SD = 2.8, N = 11) (Table 1). Similarly to the male FSL, as expected, no significant difference was found in baseline preference between control and treatment groups. An independent-samples *t*-test on the test day did not show significant differences between the two treatment conditions. (Vehicle: M = 87.8, SD = 5.7, N = 9; CBD: M = 89.6, SD = 4, N = 10) (Table 1).

For the male WKY (vs. Wistar controls) in the FST, a two-way MANOVA was performed on the variables: immobility and swimming. The MANOVA performed on the variables: immobility and swimming. The MANOVA performed on the variables: immobility and swimming. The MANOVA revealed a significant main effect of strain ($F(2,50) = 11.772$, $p < 0.001$) and an interaction of strain x drug ($F(2,50) = 8.75$, $p < 0.01$).

Tests for simple main effects with Bonferroni adjustment showed that WKY treated with vehicle were significantly more immobile ($p < 0.05$) than Wistar rats treated with vehicle, as in previous studies (e.g., [23]). In addition, WKY rats treated with 30 mg/kg CBD were significantly less immobile ($p < 0.001$) and swam significantly more ($p < 0.001$) than WKY rats treated with vehicle (Fig. 1a & 1b).

For the analysis of the female WKY, one way MANOVAs performed on the variables: immobility and swimming, revealed a significant effect of CBD ($F(2, 18) = 6.318$, $p < 0.01$). Tests for simple main effects with Bonferroni adjustment showed that CBD significantly reduced immobility and increased swimming (Fig. 2).

For the female FSL, one-way MANOVAs performed on the variables: immobility and swimming, revealed no significant effects of CBD (Fig. 3a).

For the Male FSL, one way MANOVAs performed on the variables: immobility and swimming, revealed a significant effect of CBD ($F(2, 27) = 6.005$, $p < 0.01$). Tests for simple main effects with Bonferroni adjustment showed that CBD significantly reduced immobility, but not swimming (Fig. 3b).

The current experiments indicate that oral administration of 30 mg/kg of CBD has the potential to reduce depressive-like behavior in two different genetic models of depression – WKY and FSL rats. Additionally, we extended recent findings on the pro-hedonic effects of the same dose of CBD in male WKY rats to females, strengthening the accumulating evidence for CBD as a pharmacotherapeutic agent for MDD.

The addition of the FST to the current study expands our understanding of the scope of CBD's therapeutic potential. Results of the FST demonstrated that WKY of both sexes and male FSL rats were less immobile and swam more when treated with CBD. A reduction in floating behavior suggests that depression-like symptoms such as helplessness have been improved, extending the application of the drug to alleviate these types of symptoms. Female FSL rats however did not display any change in behavior as measured by the FST. There is little research on female FSL as a model of depression and since we did not compare them to a control strain in this study we cannot conclude whether their floating levels were indicative of healthy control levels, or rather, if they modeled pathological coping behavior. Therefore, it is difficult to draw conclusions on the effects of CBD using this model. It is plausible that the lack of effects are similar to those demonstrated with Wistar controls who seem not to be significantly affected by 30 mg/kg of CBD. However, a control strain (Wistar) was only employed in the male WKY experiment, to follow the design of our previous study in male WKY rats [41]. Interpretation of the results should consider that the FST is a controversial test for females, and that males and females may be responsive to different doses of the same drug [20]. While this may hold for the FSL strain, in our current study WKY females were responsive to this dose of CBD in a similar manner as male WKY rats.

While several studies [9,36,39,40,45] have reported a similar effect

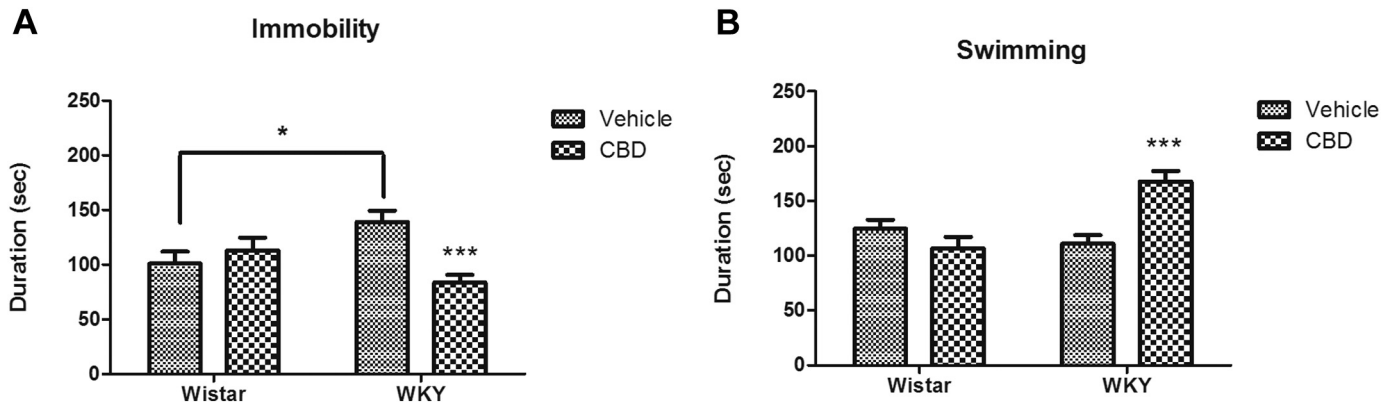

Fig. 1. A) Duration of immobility (mean + SEM) in the FST of male Wistar Kyoto (WKY) rats that received orally vehicle or 30 mg/kg cannabidiol (CBD) (N = 12 and 13 rats, respectively) versus Wistar control male rats that received vehicle or cannabidiol (CBD) (N = 13 and 17 rats, respectively). ***p < .001. B) Duration of swimming (mean + SEM) in the FST of male WKY rats that received orally vehicle or 30 mg/kg CBD (N = 12 and 13 rats, respectively) versus Wistar control male rats that received vehicle or CBD (N = 13 and 17 rats, respectively). ***p < .001.

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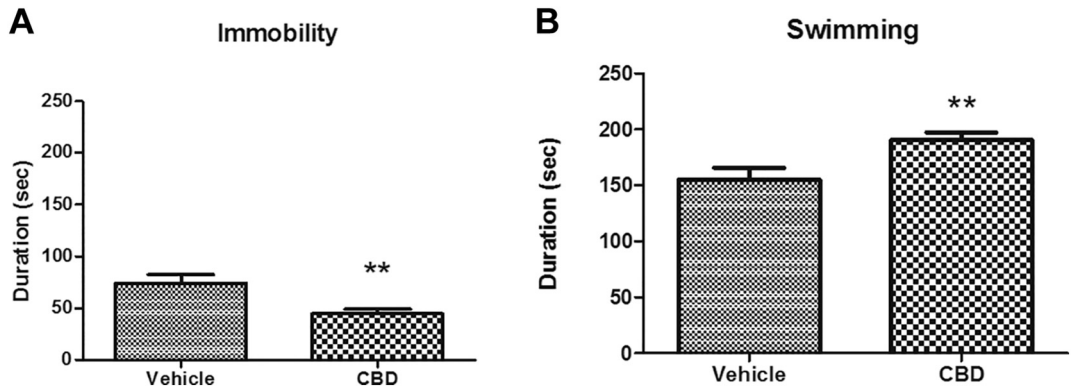

Fig. 2. A) Duration of immobility (mean + SEM) in the FST of female WKY rats that received orally vehicle or 30 mg/kg CBD (N = 9 and 12 rats, respectively). **p < .01. B) Duration of swimming (mean + SEM) in the FST of female WKY rats that received orally vehicle or 30 mg/kg CBD (N = 9 and 12 rats, respectively)). **p < .01.

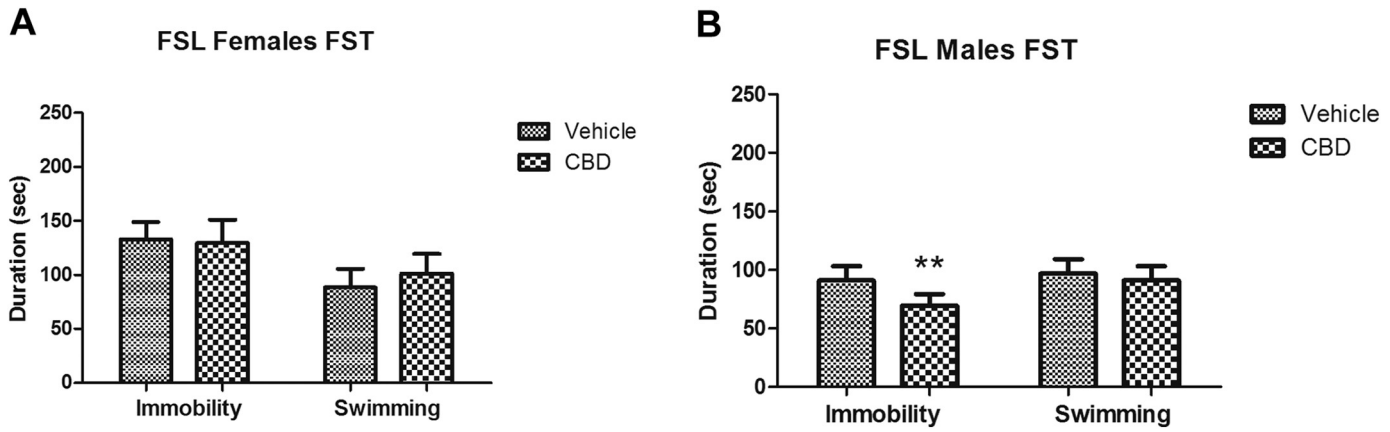

Fig. 3. A) Duration of immobility and swimming (mean + SEM) in the FST of female Flinders Sensitive Line (FSL) rats that received orally vehicle or 30 mg/kg cannabidiol (CBD) (N = 12 and 13 rats, respectively). B) Duration of immobility and swimming (mean + SEM) in the FST of male FSL rats that received orally vehicle or 30 mg/kg CBD (N = 12 and 13 rats, respectively). **p < .01.

for CBD in their studies, using males of wild-type strains of mice or rats, the present study was the first to show this anti-depressant effect in specific genetic models of depression. Both the WKY and the FSL are considered valuable models for studying depression, presenting many behavioral and physiological endophenotypes that are often present in MDD, without the need to use stress protocols to render them "depressed" [23,27].

Interestingly, although Réus et al.'s [36] study used intraperitoneal injection (IP), and the present study used oral administration, it was the same dose of 30 mg/kg, out of several doses, that had an observable effect. This indicates that even though the CBD in our study had to be absorbed via the gut before entering blood circulation, most of it remained as effective as in an IP injection, yet avoiding the stress associated with injection. Taken together, these technical aspects strengthen the findings of our research, setting this dose of CBD, per os (orally), as a potential therapeutic for MDD. In humans, the active dose of CBD in some disease states is extremely high. In schizophrenia, for example, Leweke et al. [21] found that the effective dose is about 800 mg/day. Therefore, the development of more potent CBD-type compounds is desirable.

The current study explored another key symptom in MDD: the diminished interest or pleasure in activities (DSM-5, [1]). This phenomenon, known as anhedonia, is a symptom that often appears in several different mental illnesses. A classic test for assessing this in rodents is the Saccharin Preference Test (SPT). As found in our previous study with male WKY rats [41], the current study replicated the pro-hedonic effect of 30 mg/kg of CBD with WKY females, strengthening CBD's potential use to treat disorders with anhedonic symptoms.

Although FSL rats are considered a genetic model of some aspects of depression, in contrast to WKY, they do not consistently show anhedonia-like behavior [28]. While use of relatively extreme stressors, and comparison to a relatively extreme control strain can produce anhedonia-like behavior in FSL rats, less extreme conditions and comparison with a wild-type (Sprague-Dawley) strain do not [23,33]. Thus, under the present testing conditions it was expected that the pro-hedonic effect that was found with the WKY model would not be present in the FSL model. Future studies should attempt to replicate this effect using different methods to attain convergent validity.

This study was limited to surveying the acute effects of a single CBD administration; considering that MDD is a chronic condition, the results should be interpreted carefully. Further translational experiments are needed to explore the long-term effects of chronic CBD exposure. A chronic study would reveal the potential changes in the brain that mediate the behavioral effects. In addition, investigating CBD's mechanisms is necessary in order to understand its action and its safety profile [8]. The research presented here is the first to use two different genetic rat models of depression, the WKY and the FSL rat strains, using two divergent behavioral tests both in males and females.

In conclusion, the current results provide additional support to previous data indicating that CBD may be a promising novel drug for treating depression, a prevalent condition for which new therapeutic approaches are necessary. It is plausible that CBD may also be of clinical value in other disorders with prominent symptoms of helplessness and/or anhedonia. Hence, CBD should be considered a viable

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psychopharmacological agent with the potential to relieve two relatively common symptoms of mental illness.

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