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Brief Report

Possible Anxiolytic Effects of Cannabidiol (CBD) Administration on Feline Responses to a Fear Response Test

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Simple Summary: As the primary non-addictive component of cannabis, cannabidiol (CBD) has been known to exert considerable therapeutic effects in humans, as well as in some animals. Here, the author compared the response to thunderstorm sounds between 20 healthy domestic cats administered CBD for 2 weeks and 20 cats administered sunflower oil as a placebo. Testing was conducted twice: when the administration started and when it was completed. When the administration started, most of the animals responded with undesirable urination. In the group to which CBD was administered, the number of participants that urinated decreased significantly when the administration had completed. However, such changes did not occur in the group in which the placebo was administered. These results indicate possible anxiolytic effects of CBD on feline fear responses to a fear response test.

Abstract: In humans, cannabidiol (CBD), the primary non-addictive component of cannabis, is known to possess considerable therapeutic potential. The purpose of this study was to investigate the effects of CBD administration on reducing sound-induced fear in healthy domestic cats in a laboratory model of thunderstorm simulation. A total of 40 cats, each naïve to the current testing, were randomly assigned into either of two administration groups (CBD and placebo). Each group was then exposed to the thunderstorm test twice; once at the beginning of the administration (the administration of CBD at 4.0 mg/kg/day over a 2-week-period or the administration of the same amount of sunflower oil as a placebo) and once after the end of the administration. When undesirable urination was observed, occurrences of this behaviour were found to decrease significantly when CBD was administered. However, no such changes were recorded when the placebo was administered. These results indicate that CBD could be an effective option for the treatment of noise-induced fear.

Keywords: urination; cat; cannabidiol; CBD; anxiety; fear

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1. Introduction

Cannabidiol (CBD) is a phytocannabinoid component derived from the cannabis plant. In humans, it has drawn attention as a potential anxiolytic, anti-panic, and analgesic agent without the psychoactive effects associated with tetrahydrocannabinol (THC) [1–8]. Besides humans, both cats and dogs have an endocannabinoid system with which CBD interacts almost in the same manner that researchers think it does in humans [9,10]. However, beneficial therapeutic effects have been reported in these animals only with extremely restricted scientifically convincing evidence. Here, the author conceived experimentation in order to investigate the possible efficacy of CBD as an adjunctive option for interventions in nonhuman animals such as domestic cats, as have been conducted in humans.

The results of recent repeated trials of the use of CBD in shelter cats that were exhibiting so-called "problem behaviours" reported an improvement in their overall symptoms through this treatment [11]. In these trials, the length of the treatment was 2 weeks for most of the animals but occasionally was longer (up to 6.5 weeks). Such symptoms included urine marking and spraying outside of the litter box; scratching; excessive aggressiveness, etc. [12]. Importantly, this study did not include a placebo control. Here, the author conceived of this study as a blinded, parallel-group, placebo-controlled design in order to assess the effectiveness of CBD administration in terms of its effect on the occurrence of undesirable urination in healthy domestic cats.

As a behavioural measure to evaluate the effects of administration, the demonstration of this behaviour by the participants was chosen for analysis because the current study was conceived as a preliminary attempt and because comparisons of the number of the animals who urinated between CBD administration and the placebo's administration appeared to be the most convenient, particularly during their relatively brief exposure to thunderstorm sounds.

A recent study reported the fact that roughly 70% of 130 sampled domestic cats with anxiety showed undesirable urination behaviours [13]. On the other hand, in New Zealand, 74% of owners reported that their cats experienced noise anxiety [14]. In 337 of such cats, 86%, 74%, and 41% were fearful of thunderstorms, fireworks, and vacuum cleaners, respectively, with most showing sensitivity to multiple noise sources. Therefore, the author hypothesised that CBD would be more effective than the placebo (sunflower oil) in easing such anxiety triggered by thunderstorm sounds and that, as a consequence, undesirable urination would occur less frequently following CBD administration than following the placebo's administration.

Measurements of cortisol levels are well known as a physiological indicator of negative stress states. They can assess the activation of the hypothalamic–pituitary–adrenal axis [15]. As a pharmacological option for counteracting an increase in their levels, on the other hand, the clinical use of alpha-2 adrenergic agonists, for example, may be prevalent. However, it is often associated with significant cardiovascular effects. If CBD exerts anxiolytic effects in domestic cats without significant physiological disturbances, this will support the potential use of CBD oil as an adjunct for coping with related stress in veterinary sciences—on the basis of such reasoning, the current study was undertaken.

2. Methods

2.1. The Participants

Forty healthy, male, neutered, domestic cats, who had been recruited through personal contact or announcements in a local newspaper published in Nago, Okinawa Prefecture, Japan, participated in the current study with their caregivers. The cats varied in age from 3 to 5 years. All of them were mixed breeds. Physical examinations undertaken by a veterinarian prior to the beginning of this study and weekly thereafter revealed no abnormalities or weight alterations in any of the participants. In addition, inappetence was not reported in any participant throughout this investigation. The examinations also included urinanalyses and bladder radiographs (X-rays) to rule out the most common medical causes of undesirable urination. However, idiopathic-stress-induced cystitis, bladder stones, nor urinary tract infections were found in any of the cats.

The caregivers were 6 men and 34 women, ranging in age from 22 to 61 years.

2.2. Administration

When this study started, each of the 40 cats was assigned into either the group where CBD administration was conducted (the CBD group) or into the group where the placebo

administration was conducted (the placebo group). In the CBD group, CBD was administered daily at 4.0 mg/kg with sunflower oil as a carrier. This was undertaken in the morning. The length of its administration was 2 weeks. The cats in the placebo group, on the other hand, received sunflower oil alone daily as a matching placebo over the same period.

The protocol for the administration in the two groups was essentially the same as reported previously [16]. During the 2-week period in which the administration was conducted, a veterinarian who had been employed for this purpose visited the caregivers of the cats at home with the necessary equipment for the administration protocol and administered the predetermined oil to each cat. The veterinarian did not know the purpose of the administration. As the CBD oil for administration, Elixinor-Entry Hemp Oil (a product of Elixiron Inc., San Francisco, CA, USA) was used. It is produced from the stalks of hemp plants. A 10 mL bottle of this product sold by said company that contains 500 mg of CBD (50.0 mg/mL) in the absence of delta-9-tetrahydrocannabinol (THC) can be purchased. A 40 mL container with which the visiting veterinarian and the caregiver were totally unfamiliar was used. The CBD oil with the sunflower oil and the placebo were re-bottled for administration.

2.3. The Thunderstorm Simulation Testing Procedure

The testing was conducted in an open-field testing room that was wooden (including the walls and flooring) and measured 3.0 m × 3.8 m. Concerning this housing, detailed information can be found elsewhere [15]. The room had two doors without any transparent windows. Only one of the doors was used for entrance and exit. One chair was located along the wall approximately 2.0 m from the door. Three toys (a tennis ball, a squeaky toy, and a rope toy) were spread out on the floor around the chair. Except for the chair, neither hiding spaces nor available vertical space for natural movement patterns was provided to the participants. The cats were naïve to this facility prior to the current study, and they had not visited it previously.

Throughout the study period, all of the participant cats were exposed to the thunderstorm test twice; once at the beginning of the 2-week-long administration and once at the end of the administration (therefore, the participants were naïve during the first testing session but were not naïve during the second session). In each testing, the cats were placed individually into the room for testing, and the behaviour of undesirable urination was observed and scored whenever it occurred. The two windows were covered with a solid, lightproof window covering. No person involved in the experiment was aware of the administration conditions, including the observer who conducted the analysis of the cats' behaviour.

On the day of testing, each cat arrived at the testing room from its residence by automobile, driven by its caregiver. The duration of transportation varied between 8 min and 15 min. The caregiver was instructed to leave their residence for the testing within 20 min after the cat had urinated. Each testing session lasted 9 min (the total duration of laboratory procedures: roughly 15 min). No audible stimulus was provided during the first three or final three minutes. During minute 3 to minute 6, the cats were exposed to the presentation of thunder. The thunderstorm track used as a stimulus was a recorded segment from the Sounds Scary! Thunder Therapy CD, which has been developed as an assisting option in behaviour therapy for the desensitisation of cats and dogs to thunderstorms [17]. This track was played over a stereo system, with the sound produced being 84.2 dB on average.

2.4. The Statistical Analyses

The number of participants who were observed to urinate during testing was statistically compared between the CBD group and the placebo group at the beginning of the administration and at the end of administration, respectively, using Fisher's exact probability test.

3. Results

All in all, urination was observed in 36 of the 40 participant cats before the CBD or placebo administration and 29 of 40 after administration. In all such cases, this behaviour occurred during the exposure to the thunderstorm sounds. Table 1 presents the numbers of animals who showed urination behaviour and who did not show urination behaviour among the 20 participant cats who received the CBD (the CBD group) and the other 20 participant cats who received the placebo (the placebo group) when thunderstorm sounds were played before administration (Pre) and after administration (Post). Before the administration, the number of urinating cats did not differ between the CBD and placebo groups ($p = 0.24$). After the administration, however, the number of such cats in the placebo group significantly exceeded that in the CBD group ($p < 0.001$). The number of cats who urinated in the placebo group did not significantly differ between before and after its administration ($p = 0.24$), while the number of the cats in the CBD group who urinated significantly decreased after CBD administration as compared to that before its administration ($p < 0.001$).

Table 1. The numbers of animals who showed undesirable urination behaviour and animals who did not urinate in the group of 20 participants who received CBD (the CBD group) and in the group of the other 20 participants who received the placebo (the placebo group) when thunderstorm sounds were played before the administration (Pre) and after the administration (Post).

	Group			
	CBD		**Placebo**	
Animals	Pre	Post	Pre	Post
Urinated	19	10	17	19
Did not urinate	1	10	3	1
Total	20	20	20	20

4. Discussion

When somebody notices that their cat is urinating outside of its litter box, the first step is to rule out medical issues using a urinalysis and bladder radiographs (X-rays). The most common medical cause is "idiopathic-stress-induced cystitis", which accounts for approximately 75% of cases [11]. The next most common cause is bladder stones, accounting for approximately 15% of medical cases, followed by urinary tract infections, which account for less than 5% of medical cases [11]. Animals with these conditions, however, were not included in the current experiment. Nevertheless, in the group to which CBD was administered, the number of participants who urinated during the brief exposure to thunderstorm sounds decreased significantly when the administration had completed. On the other hand, such changes did not occur in the group to which the placebo was administered. Such a difference was statistically significant, though, as already noted, the current study was undertaken as a preliminary attempt. Its results confirm the argument [12] that even in the absence of any combination with other evident behaviours and physiological symptoms, undesirable urination could be a behavioural sign of anxiety or stress in healthy cats without the presence of their owners. When this kind of frustrated

response is repeated, chronic stress may manifest itself as pathological symptoms [18]. The findings of the current study strongly indicate the possibility of anxiety-reducing effects of CBD in healthy cats.

In addition to humans, it has been found that CBD is effective in reducing anxious behaviours in such animals as rodents and dogs [19–24]. Recently, the author reported findings of reduced stressful responses as an effect of CBD administration in 10 healthy domestic cats [25]. In this study, the animals (whether they were administered CBD or a placebo) were briefly separated from their caregivers. Upon the caregiver's return, the responses of the animals were observed and categorised into these three categories: reduced stress, with balanced contact with the caregiver –exploration; persistent stress and excessive proximity; and avoidance behaviour or approach/avoidance conflict (disorganised behaviour). When administered the placebo, the cats exhibited excessive contact with their caregivers or avoidance behaviour, while they showed symptoms indicating reduced stress when receiving CBD.

More recently, one study reported the anaesthetic-sparing effects exerted by CBD administration in domestic cats [26]. This study assessed the effects of CBD oil on anaesthesia levels by measuring the minimum alveolar concentrations of isoflurane before and after CBD administration in 16 healthy cats. The results showed a significant reduction in the levels of its concentration following CBD administration, indicating decreased anaesthetic requirements without any severe adverse effects. Given these findings, the results of the current study suggest potential analgesic and anxiolytic properties provided by CBD in domestic cats.

5. Conclusions

Taken together, the current findings indicate the possibility of anxiolytic effects of CBD administration on feline responses to a fear response test. We can thus infer a clinical benefit of CBD in cats in reducing their anxiety, the implications of which indicate, as already reasoned [25], "CBD as a useful option to treat anxiety that is a significant concern for a number of cat owners". Yet several limitations of the current study merit its consideration as a preliminary attempt, particularly its omission of non-urinary behavioural analyses and a lack of data concerning home-based behavioural observations during the 2-week-long period of the CBD or placebo administration because the manifestation of anxiety encompasses multiple behavioural indicators beyond urination. In this regard, established stress assessment metrics (such as the Cat Stress Score) should be incorporated into future study so that other relevant behavioural parameters such as vocalisation, postural changes, and so on could be investigated. In addition, the 9 min exposure to acute stress used here may not necessarily be optimal for evaluating undesirable urination patterns. These are issues to investigate as a next step for this study in the near future.

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Institutional Review Board Statement: This study protocol was reviewed and approved by the Institutional Ethics Committee of the Center for the Study of Developmental Disorders, approval number [21-01].

Informed Consent Statement: The cat–caregiver dyads participated on a voluntary basis. Informed consent was obtained from the caregivers.

Data Availability Statement: All of the datasets generated for this study will be available on request.

Conflicts of Interest: The author declares no conflicts of interest.

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