RESEARCH ARTICLE

The Effect of Delta-9-Tetrahydrocannabinol and Cannabidiol on Blood Flow

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Abstract

Background: This study is based on the premise that while consumption of cannabis has increased for medicinal and recreational purposes there has also been an increase in adverse events seemingly associated with cannabis usage.

Objective: This study was designed to investigate the effect of different concentrations of Delta-9-Tetrahydrocannabinol (THC) and Cannabidiol (CBD) separately and in combination on blood flow.

Method: Forty male Sprague-Dawley rats were randomly divided into eight groups consisting of five rats each. Six of the test groups received different concentrations of THC and CBD (1 and 2 mg/kg body weight) respectively, while the seventh group received an extract with a combination of THC and CBD (2 mg/kg body weight) in a one to one ratio. The control group received the vehicle only. Drugs were administered intraperitoneally on alternate days for five days. Blood flow readings were taken at 0, 15, 30, 45 & 60 minute intervals using the CODA non-invasive blood pressure system.

Results: The results indicate that blood flow decreased with increasing THC concentration and was significant ($p < 0.05$) at 45 minutes with 2 mg/kg dose. CBD caused an increase in blood flow with increasing concentrations and this was also significant ($p < 0.05$) at 45 minutes with 2 mg/kg dose. The extract however caused a non-significant decrease in blood flow.

Conclusion: The results suggest that THC and CBD have opposing effects on blood flow separately, but when used in combination THC seems to exert a greater effect on blood flow than CBD.

Keywords: blood flow, cannabis, extract, THC, CBD

1. INTRODUCTION

Delta-9-Tetrahydrocannabinol (THC) and Cannabidiol (CBD) are two of the most well-known phytocannabinoids which can be obtained from the trichomes distributed across the surface of the cannabis plant. They represent two of the more than one hundred and fifty cannabinoids found in the cannabis plant [1]. THC is believed to be widely responsible for the psychoactive effect that is experienced on using the plant or its components while CBD is non-psychoactive and able to modulate the effects of THC when they are used in combination [2].

Widespread legalization of cannabis in recent years has resulted in its increased usage for both recreational and medicinal purposes. As a result, there are currently more than 188 million cannabis users worldwide [3]. The concern however is that cannabis is known to have both therapeutic as well as deleterious effects. The extent of the effect experienced whether positive or negative appear to be dependent on the cannabinoid composition of the particular cannabis plant or section of the plant used and in particular, the THC to CBD ratio present [4]. As a result of the possible variations in cannabinoid content the use of cannabis for medicinal purposes therefore require standardization. It is important to point out that when whole plant preparations are used or consumed, the magnitude of the effects experienced may not only be dependent on the cannabinoids present but may also be affected by other components present such as terpenes [4].

In addition to the consideration that must be given to the cannabinoid content of the cannabis preparation to be used, particular attention must also be paid to the route of administration as this will influence the bioavailability of the active components as well as the time frame within which they are most effective [4]. Cannabis has been documented to exert a variety of effects which can be classified as either behavioural, physiological and psychological effects. Cannabis has been approved in various dosage forms and in several countries for the treatment of anorexia in AIDS patients, to combat nausea and vomiting after chemotherapy in cancer patients and for treatment of neuropathic pain for individuals suffering from neurological disorders [5]. Various clinical trials have also been conducted to evaluate the effect of THC and CBD in the treatment of a variety of disorders, which have yielded variable effects.

In recent years however, increasing correlation has been found between cannabis utilization or consumption and adverse cardiovascular events such as arteriopathy, stroke and acute myocardial infarction. These adverse events have occurred both in young adults with no underlying predisposing factors and in older adults with underlying risk factors [4]. Based on literature, different vascular and circulatory responses have also been observed in different animals depending on the cannabinoid or combination of cannabinoids used, the dosages that are administered and even the specific vascular bed being studied [6]. As a result, both vasodilation and vasoconstriction have been observed leading to some of the potentially therapeutic or deleterious effects as mentioned above. Therefore, while it is important to highlight the beneficial effects of cannabinoids, careful consideration also has to be given to the possible negative effects. Given the increased usage of cannabis for recreational and medicinal purposes, this study seeks to determine the effect of THC and CBD separately and in combination on blood flow.

2. MATERIALS AND METHODS

2.1.Sample Preparation

THC and CBD were obtained from Biotech R & D Institute. Stock solutions were

prepared using 5% ethanol to obtain final concentrations of 1 and 2 mg/ml.

2.2.Subjects

Forty male Sprague-Dawley rats (200 - 250 g) were obtained from the Animal House, University of the West Indies, Mona. The animals were fed daily with a standard rat diet and water *ad libitum* and kept on a 12-hour light/ 12-hour dark cycle for the duration of the study.

The animals were allowed one week to acclimatize to the laboratory conditions before the start of experimental procedures. Experiments were conducted in accordance with the guidelines and regulations stipulated by the UHWI/UWI/FMS Ethics Committee, UWI, Mona.

The rats were randomly divided into eight groups of five rats each. One group served as a control group, while the other seven groups served as test groups. Six of the test groups received different concentrations of THC and CBD (1 and 2 mg/kg body weight) respectively, while the seventh group received a combination of THC and CBD (2 mg/kg body weight) in a one to one ratio. The control group received the vehicle (5% ethanol solution) only. Drugs were administered intraperitoneally at an injection volume of 1mg/kg, on alternate days for five days. These concentrations were chosen based on concentrations of THC in plasma that were observed to give a psychoactive effect in previous studies [7]. A dose conversion was then done to determine the concentration that would be effective in rats [8].

Blood flow was determined prior to and after administration of THC and CBD, at fifteen-minute intervals for up to 1 hour using the CODA non-invasive blood pressure system (Kent Scientific Corporation).

On completion of the experimental procedures each animal was euthanized using 120 mg/kg sodium pentobarbitone given intraperitoneally and their carcasses stored in the University of the West Indies Animal House deep freezer for subsequent incineration.

2.3.Data Analysis

The results were analysed using the SPSS software (version 20). They were expressed as means ± standard error of the mean (SEM). Repeated measures Analysis of variance (ANOVA) was used to determine the difference between the means obtained. The statistical significance was taken at the 95% confidence interval a p value of <0.05 was considered to be significant.

3. Ethical Approval

Ethical approval for the study was obtained from the UHWI/UWI/FMS Ethics Committee, UWI, Mona.

4. RESULTS

THC caused a decrease in blood flow with increasing concentration and this was significant ($p < 0.05$) at 45 minutes with the 2 mg/kg concentration (17.2 ml/min for the control and 6.4 ml/min for 2 mg/kg) (Figure 1).

Blood flow increased with increasing concentrations of CBD and this was also only significant ($p < 0.05$) at the 45-minute interval with the 2 mg/kg concentration (17.2 ml/min for the control, and 24.1 ml/min for 2 mg/kg) (Figure 2).

The extract caused a decrease in blood flow which was not significantly different from the control (Figure 3).

A comparison of the changes in blood flow over time for CBD, THC and the extract showed that the extract had an effect that was midway between that of CBD and THC (Figure 4).

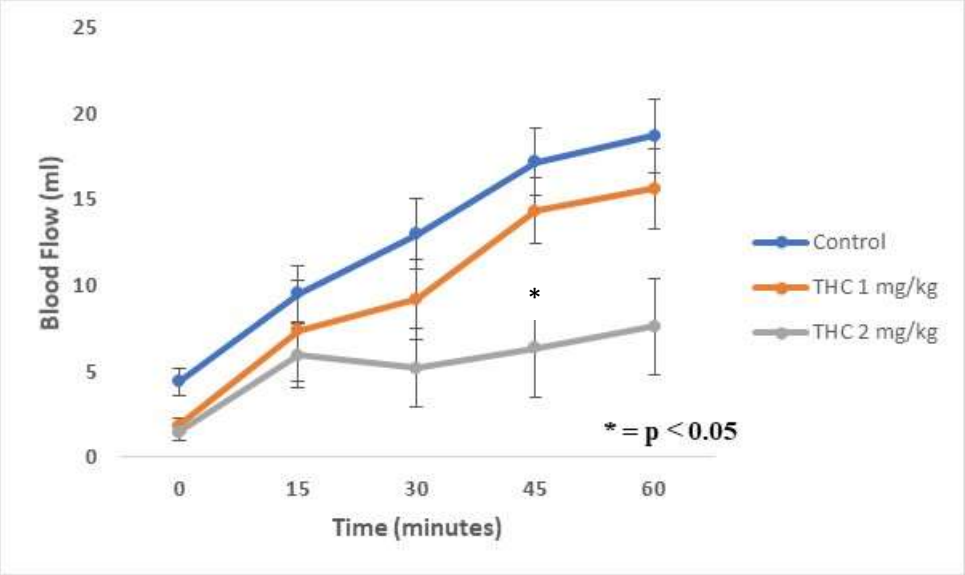

Figure 1. The effect of 1 and 2 mg/kg concentrations of THC on blood flow. Changes were assessed by means of repeated measures one-way analysis of variance (ANOVA). Values are expressed as means for plots, n = 5. *p indicates significant difference from control at $p < 0.05$.

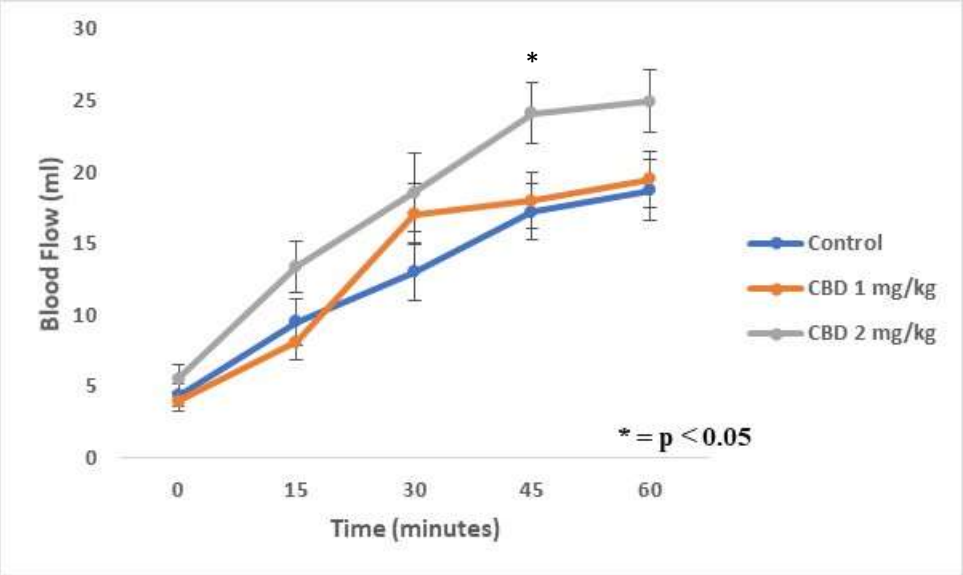

Figure 2. The effect of 1 and 2 mg/kg concentrations of CBD on blood flow. Changes were assessed by means of repeated measures one-way analysis of variance (ANOVA). Values are expressed as means for plots, n = 5. *p indicates significant difference from control at $p < 0.05$.

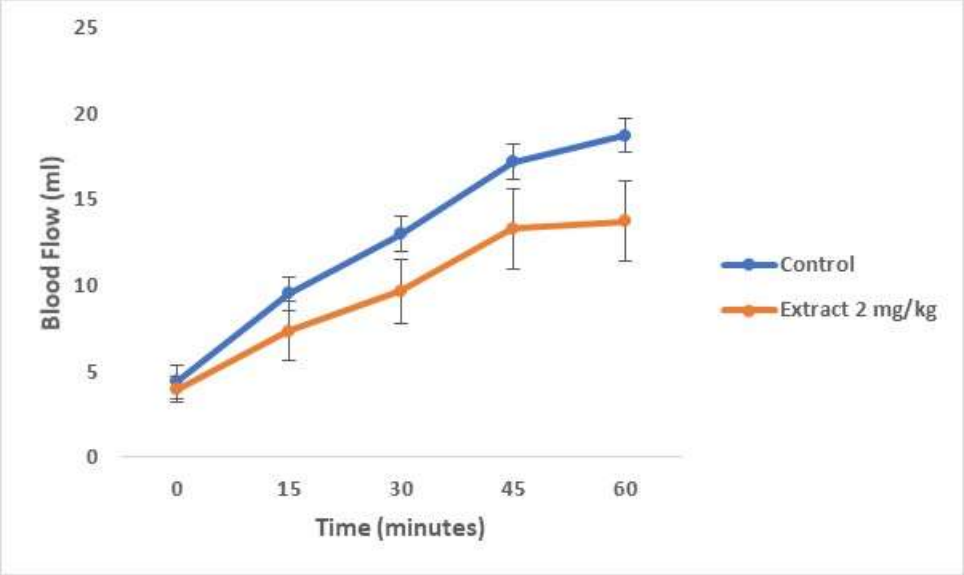

Figure 3. The effect of a cannabis extract containing a 1:1 ratio of THC to CBD on blood flow. Changes were assessed by means of repeated measures one-way analysis of variance (ANOVA). Values are expressed as means for plots, n = 5.

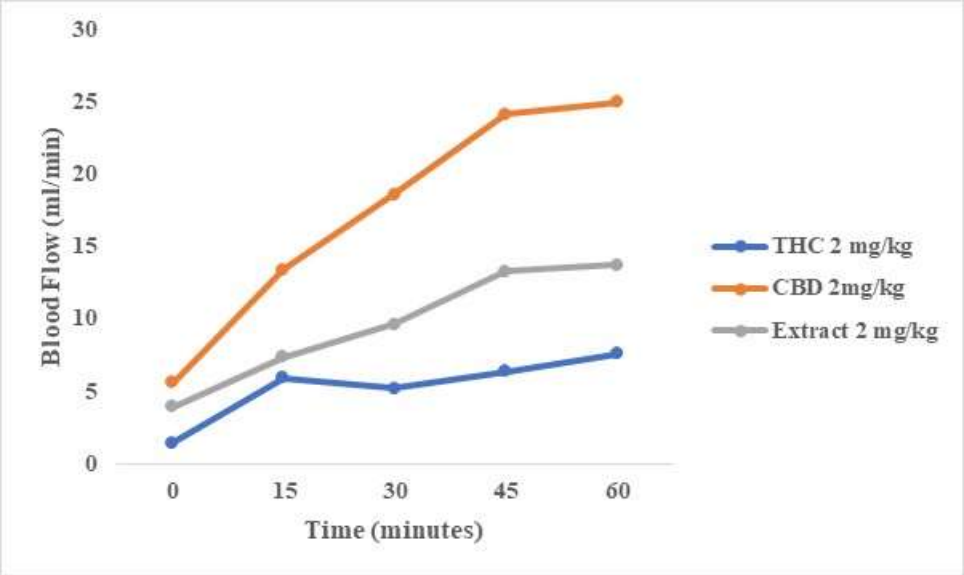

Figure 4. The effects of similar concentrations of THC, CBD and a 1:1 cannabis extract on blood flow. Changes were assessed by means of repeated measures one-way analysis of variance (ANOVA). Values are expressed as means for plots, n = 5.

5. DISCUSSION

The results of this study show that THC caused a decrease in blood flow with increasing concentrations. Cannabis is believed to cause vasoconstriction in some arterial systems although this is not universal to all vascular beds [4]. This has led to some adverse cardiovascular effects which include arteriopathy, stroke and acute myocardial infarction. It is also believed that cannabis is a source of cellular oxidative stress which can lead to arterial vasospasm [4]. Based on the above-mentioned either vasoconstriction or

vasospasm could have led to the decreased blood flow observed with increasing concentrations of THC. THC has also been found to cause a decrease in cerebrovascular blood flow believed to be due to transient vasospasm either separately or in conjunction with an increased central blood pressure, resulting in decreased cerebral blood flow [9].

On the other hand, the results indicate that blood flow increases as CBD concentration increases. Cannabis is believed to cause an acute vasodilatory response under controlled experimental conditions although this is not universal to all vascular beds [4]. This vasodilatory response could be the reason for the increased blood flow observed with increasing concentrations of CBD. CBD has also been found to increase blood flow under ischaemic conditions and during strokes in animal models [10]. Other studies have also reported that CBD usage could result in vasorelaxation in both human and animal studies after acute and time dependent administration [11]. This contrasts with previous studies that have found that CBD had no effect on blood flow under control conditions [12] or baseline cardiovascular parameters [11]. Cannabis usage has been found to result in diminished cerebral autoregulatory capacity and as a result both increases and decreases in regional cerebral blood flow have been observed in studies conducted to determine the impact of cannabis usage. Both THC and CBD may be able to offer neuroprotection after strokes while several other studies have found a link between cannabis usage and the occurrence of strokes [13]. The effect of cannabinoids on the circulatory system appear to be dose dependent and cannabinoids may either increase or decrease blood flow in different areas of the circulatory system [14], The increases in blood flow observed in this study was only significant when 2 mg/kg CBD was used at the 45-minute interval, indicating that the effect of THC and CBD are both dosage and time dependent.

While the effect of both THC and CBD would likely have been evident beforehand, the peak effect appears to occur during the 45-minute interval when the decrease or increase in blood flow was significant. This seems to be in line with the pharmacokinetics of THC after oral administration. When orally administered, the delayed onset of the effects of cannabis can usually be seen within 30 to 130 minutes [15]. This can be attributed to acid degradation in the stomach and an extensive first pass metabolism by the liver, which reduces oral bioavailability [16]. In this case however, THC and CBD were administered intraperitoneally. Substances administered by this route have been observed to behave similarly to oral administration because they are primarily absorbed into mesenteric vessels and therefore pass through the liver where they undergo first pass metabolism before they go into systemic circulation [17].

Similar to THC, the cannabis extract caused a decrease in blood flow which was not statistically significantly at any of the time intervals. The decrease in blood flow which occurred indicates that when used in combination THC exerts a greater effect than CBD when used in a one-to-one ratio. The different effects of cannabinoids on various vascular beds is believed to be due to different mechanisms within the vascular beds which bring about endothelial vasodilation [4]. Previous studies have also determined that vasodilation may occur as a result of the activation of vascular cannabinoid receptors [18].

Whereas the physiological and therefore cardiovascular effects of cannabis are believed to be primarily mediated by the G protein coupled receptors namely CB1 and CB2 of the endocannabinoid system, the effects of THC have been found to be primarily effected through CB1 receptors located within the central, autonomic and peripheral sensory nervous systems [4]. It therefore has an impact on multiple systems throughout the body due to its extensive

distribution [19]. CBD on the other hand has been found to antagonize both CB1 and CB2 receptors at very low concentrations (nanomolar range) but can also act as an agonist at higher concentrations (micromolar range) [10].

On the other hand, both cannabinoids have been found to interact with several other receptors and in fact cannabis has been found to cause vasodilatory effects through activation of transient receptor potential ankyrin type 1 ion channels (TRPA1). Vasoconstriction has however been seen in peripheral, cerebral and coronary artery systems with the differing effects depending on the different vasodilator mechanisms within a given artery, resulting in the opposing effects of cannabis observed in different vascular beds [19]. Furthermore cannabis usage has also led to regional arterial vasospasm through activation of CB1 receptors via endothelial dysfunction arising from the generation of reactive oxygen species [4]. These differing effects could explain the opposing effects of THC and CBD as observed in this study.

Administration of THC and the extract caused blood flow to decrease and therefore could result in deleterious effects for cannabis users. CBD on the other hand was able to increase or maintain blood flow and therefore could prove beneficial in some adverse conditions such as in the case of a stroke. Taking these factors into consideration we can therefore see that where athletes are concerned, the ingestion of either pure THC or a combination of THC with other cannabinoids could prove detrimental to their performance, whereas CBD could be beneficial. However, since cannabis is currently banned in the field of athletics, there are no standardized preparations of pure CBD for this purpose, and until further specific research into this area is conducted, its usage could not be advised. Furthermore, there would also be the danger of athletes consuming cannabis products with uncertain content and this could impact their performance in a negative manner.

6. CONCLUSION

The changes observed with different concentrations of THC and CBD indicate that they have opposing effects on blood flow. Increasing concentrations of THC caused a significant decrease in blood flow while increasing concentrations of CBD caused a significant increase in blood flow. When used in combination as in the extract there was an effect that is more in line with the individual effect of THC where there was a decrease in blood flow, though not statistically significant.

When used separately THC and CBD exhibit different effects on blood flow, but when used in combination the effect of THC seems to modulate the effect of CBD. This has implications for their use recreationally and medicinally.

7. Acknowledgements

Tameika James was involved in the design of the study, carried out the data acquisition and analysis and was involved in preparing the manuscript. Charah Watson has made substantial contributions to the design and coordination of the study. Dagogo Pepple was instrumental in the conception, design and coordination of the study as well as the critical review of the paper.

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Declaration of interest (Disclosures):
None

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