ORIGINAL RESEARCH PAPER

Volume-8 | Issue-2 | February-2019 | PRINT ISSN No 2277 - 8179

INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

ANTI-INFLAMMATORY EFFECTS OF CANNABINOID 2 RECEPTOR AGONIST, GW405833, IN A MODEL OF CARRAGEENAN-INDUCED ACUTE INFLAMMATION OF THE RAT PAW

Pharmacology

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ABSTRACT

The aim of this study is to investigate the anti-inflammatory effects of selective CB2 receptor agonist, GW405833, in the carrageenan or capsaicin paw edema test of rats. Mix type of inflammation was induced by giving an intraplantar injection of carrageenan or neurogenic type of inflammation was induced by giving an intraplantar injection of capsaicin into the paw. Paw thickness was measured with electronic digital calipers, prior to and 1 or 4 h following administer of capsaicin or carrageenan respectively, which corresponds to peak edema time. Pretreatment of rats with both GW405833 and diclofenac significantly attenuated carrageenan- or capsaicin-induced paw edema compared to vehicle-treated group and carrageenan- or capsaicin-treated group. CB2 receptor antagonist, AM630, significantly reversed the effect of CB2 agonist. The GW405833 significantly inhibited plasma extravasation in carrageenan- or capsaicin-induced paw edema. Diclofenac inhibited also plasma extravasation, but has effect as more weak. CB2 receptor antagonist, AM630, significantly reversed the effect of CB2 agonist.

KEYWORDS

Cannabinoid, inflammation, evans blue dye, rat paw.

INTRODUCTION

Cannabis sativa produces over 80 cannabinoids. Δ9-tetrahydrocannabinol (THC) is identified as the main bioactive constituent of cannabis, the main psychotropic constituent of marijuana (1). The psychological addiction resulting from the abuse of cannabis is the main concern limiting its therapeutic use (2). However nonpsychoactive compounds are available, cannabidiol (CBD) and cannabinol (CBN) (3). Basicly the researches are using several synthetic cannabinoids including Naphthoylindoles (e.g., JWH-018, JWH-073, JWH-398), Naphthylmethylindoles (e.g., JWH-175, JWH-195, JWH-197), Naphthoylpyrroles (e.g., JWH-030, JWH-156, JWH-243), Naphthylmethylindenes (e.g., JWH-176), Phenylacetylindoles (i.e., benzoylindoles, e.g., JWH-250, JWH-253, JWH-313), Cyclohexylphenols (e.g., CP 47,497 and homologs of CP 47,497), and etc (4–6).

The Receptors of Cannabinoidergic system were found and cloned in the early 1990s (7). The endogenous cannabinoid (CB) system consists of two G-protein-coupled cannabinoid i.e. CB1 and CB2 receptors (8). However there are maybe additional receptors and, some EC effects result from the interaction with other receptors, such as the vanilloid receptor. The cannabinoid CB1 receptors are preferentially located on brain and also expressed in nerve terminals of peripheral tissues including heart and vessels (9). The cannabinoid CB2 receptors are mainly located on peripheral non-neuronal cells (mostly immune system cells) which exert a broad range of critical effects under physiological or pathological conditions (10). The endogenous ligands of Endocannabinoids turned out to be fatty acid-derived molecules including Anandamide (arachidonoyl ethanolamide, AEA) and 2-arachidonoylglycerol (2-AG). AEA has more affinity to CB1 than CB2, 2-AG shows similar affinity for CB1 and CB2 (11). CB2 receptors may also bind other endocannabinoid ligands; however, the signalling consequences of this binding is poorly known. AEA is hydrolyzed mainly by fatty acid amide hydrolase (FAAH) into arachidonic acid and ethanolamine. 2-AG is synthesized from its phospholipid precursor diacylglycerol by diacylglycerol lipases (12). Phospholipase C-β releases diacylglycerol (DAG) from phosphatidylinositol-4,5-bisphosphate, which in turn is metabolized by diacylglycerol lipases (DAGLs) – with DAGLα and DAGLβ having prevalent roles in the brain and in several peripheral tissues, respectively – to produce 2-AG (12). The major degradative or inactivated pathway of 2-AG is its hydrolysis to arachidonic acid and glycerol by monoacylglycerol lipase (MAGL) (13). Although the hydrolysis pathway seems to be the primary fate of AEA and 2-AG, they can also be oxidized by cyclooxygenase-2 and lipoxygenase isozymes, thus producing oxidized endocannabinoids, which are involved in regulating brain synaptic transmission and other biological processes (14).

Accumulating evidence has indicated that EC and their major receptors CB1 and CB2 play a major role in the pathophysiology of diseases at a preclinical stage. The selective CB2 molecules are increased to interest as new targets in drug discovery. Endocannabinoids can modulate levels of proinflammatory mediators and immune cell migration (15). Exogenously administered 2-AG and anandamide or several selective agonists to animal models of inflammation have also shown to be effective. ECs are provided by a series of central and peripheral effects (16). CB1 is more responsive to psychoactive cannabinoids (eg, THC) than to nonpsychoactive cannabinoids (eg, cannabidiol) (17). ECs influence analgesia and motor function, energy balance and food intake, cardiovascular function, immune and inflammatory responses, and cell proliferation. The endocannabinoid system has been found to be involved in many inflammation-related conditions, such as Multiple sclerosis, Atherosclerosis, Inflammatory bowel disease, RA, Sepsis, and Allergic inflammation (18–20). The blockage of CB1 and activation of CB2 could inhibit inflammation in various animal models, mainly through restraining the activity of the immune system. The exogenous application of AEA and 2-AG exerts anti-inflammatory effects by decreasing the production of inflammatory mediators (21). The exogenous application of selective CB2 agonists exerts anti-inflammatory effects by decreasing the production of inflammatory mediators (16). Upregulating the level of endogenous cannabinoids by inhibiting their common metabolic enzyme, becomes an important strategy in the treatment process of inflammation-related diseases. We had evaluated some effects of the cannabinoid CB2 receptor activations' during the inflammatory processes of peripheral tissues after intestinal ischemia/reperfusion.

This study was designed to investigate the anti-inflammatory effects of selective CB2 receptor agonist, GW405833, in the carrageenan or capsaicin paw edema test of rats.

MATERIALS AND METHODS

Animals and Experimental Design:

The subjects weighed between 200 and 250g, and were housed in a temperature (20–22 °C) in their home cages and were maintained on a 12/12 h light/dark cycle. All rats were given standard rat chow and water ad libitum. The sample size for each treatment group was 6 to 8 rat/group. All animal protocols were approved by the Institutional Animal Care and Use Committee and were in accordance with the National Institutes of Health Guide for the care and use of Laboratory animals. After testing was completed, all rats were humanely euthanized via CO2 asphyxia, followed by rapid cervical dislocation.

Carrageenan-induced paw edema:

Mix type of inflammation was induced by giving an intraplantar

injection of carrageneen (50 µl, 1%) or capsaicin-induced paw edema-Neurogenic type of inflammation was induced by giving an intraplantar injection of capsaicin (50 µl, 0.1%) into the paw. Edema was expressed as the increase in paw thickness (mm) after carrageenan injection relative to the pre-injection value for each animal. Paw thickness was measured with electronic digital calipers, prior to and 1 or 4 h following capsaicin or carrageenan administration respectively, which corresponds to peak edema time.

In the first group, plasma extravasations were measured via Evans blue dye method (22). The dye was injected in the tail vein 15 min before the end of the experiments. The anaesthetized animals were sacrificed by decapitation, and hind paws were incubated with formamide for 48 h, and then the extracted dye was measured by spectrophotometry at 620 nm.

In the second group, paw thickness was measured with electronic digital callipers, prior to and 4 h following carrageenan or 1 h following capsaicin administration, which corresponds to peak edema. This procedure has been used previously by studies (16).

The anti-edematous effects of GW405833 (3 mg/kg, i.v.) were compared to diclofenac (10 mg/kg, i.v.), a nonselective cyclooxygenase inhibitor, 15 min before these intraplantar injections of inflammatory agents. CB receptor involvement in the anti-inflammatory effects of GW405833 was evaluated by administration of the CB2 receptor antagonist, AM630 (1 mg/kg, i.v., 5 min before CB2 agonist injection).

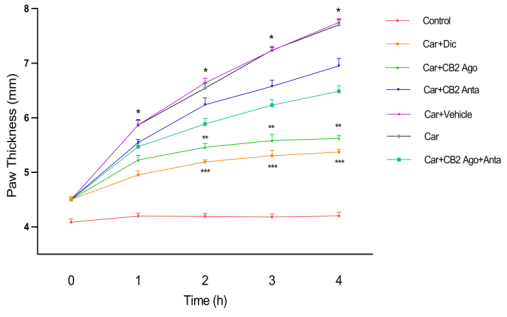
All statistical analyses were carried out using GraphPad statistical software. All data were presented as mean ± standard error mean. Difference between groups was compared using student *t* test or one-way ANOVA followed by Tukey's Multiple Comparison. $P < 0.05$ was considered significant.

RESULTS:

The carrageenan-induced paw edema

Administrate of carrageenan caused clear edema in paw tissue ($^{*}P < 0.001$). Pretreatment of rats with both GW405833 ($^{**}P < 0.05$) and diclofenac ($^{***}P < 0.001$) significantly attenuated carrageenan-induced paw edema compared to vehicle-treated group. CB2 receptor antagonist, AM630, significantly reversed the effect of CB2 agonist ($P < 0.01$) (Figure 1).

Figure 1. The carrageenan-induced paw edema and the effect of CB2 agonist.

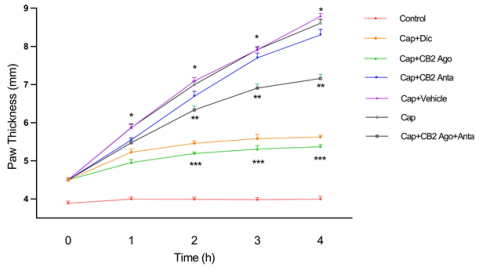


Data are expressed as mean ± S.E.M. (n= 6) and one-way ANOVA followed by Tukey's multiple range test. Carrageenan treated lead to edema (*p< 0.001) as compared to Control group, pretreatment of CB2 agonist found statistically significant (**p < 0.05) as compared to Car group and diclofenac (***p < 0.05) inhibited carrageenan-induced paw edema as compared to Car group.

The capsaicin-induced paw edema

Administrate of capsaicin caused clear edema in paw tissue (*P < 0.001). Pretreatment of rats with GW405833 (***P < 0.001) significantly attenuated capsaicin-induced paw edema compared to vehicle-treated group. CB2 receptor antagonist, AM630, significantly reversed that effect (**P < 0.001) (Figure 2).

Figure 2. The capsaicin-induced paw edema and the effect of CB2 agonist.

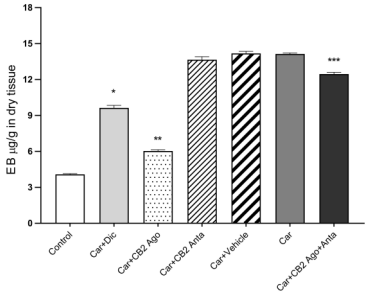


Data are expressed as mean ± S.E.M. (n= 6) and one-way ANOVA followed by Tukey's multiple range test. Capsaicin treated lead to edema (*p< 0.001) as compared to Control group, pretreatment of CB2 agonist found statistically significant (**p < 0.001) as compared to Dic group and CB2 antagonist (***p < 0.05) reversed healing of CB2 agonist (**P< 0.001).

The effect of CB2 agonist on plasma extravasation in carrageenan-induced paw edema

The GW405833 significantly inhibited plasma extravasation in carrageenan-induced paw edema (**P < 0.001) . Diclofenac inhibited also plasma extravasation, but has effect as more week (*P < 0.05). CB2 receptor antagonist, AM630, significantly reversed the effect of CB2 agonist (***P< 0.01) (Figure 3).

Figure 3. The carrageenan-induced inflammation in paw tissue and the effect of CB2 agonist on plasma extravasation.

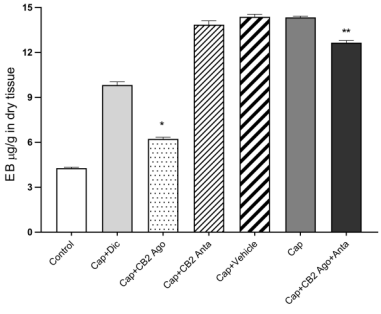


Data are expressed as mean ± S.E.M. (n= 6) and one-way ANOVA followed by Tukey's multiple range test. Diclofenac inhibited plasma extravasation (*P < 0.05), CB2 agonist significantly lead to inhibition of edema (**p< 0.001) as compared to Car group, CB2 antagonist (***p < 0.05) inhibited healing of CB2 agonist (***P< 0.001).

The effect of CB2 agonist on plasma extravasation in capsaicin-induced paw inflammation

The GW405833 strongly inhibited plasma extravasation in capsaicin-induced the neurogenic inflammation in paw tissue (*P < 0.001). Diclofenac not inhibited plasma extravasation (P > 0.05). CB2 receptor antagonist, AM630, significantly reversed the effect of CB2 agonist (**P< 0.001) (Figure 4).

Figure 4. The capsaicin-induced neurogenic inflammation and the effect of CB2 agonist on plasma extravasation.



Data are expressed as mean ± S.E.M. (n= 6) and one-way ANOVA followed by Tukey's multiple range test. CB2 agonist strongly inhibited plasma extravasation in capsaicin-induced the neurogenic inflammation in paw tissue (*P<0.001). Diclofenac not inhibited plasma extravasation (P > 0.05). CB2 receptor antagonist significantly reversed the effect of CB2 agonist (**P<0,001).

DISCUSSION

Although it is known by researchers working in inflammation that carrageenan-induced paw edema is the standard experimental model of acute inflammation. In the present study, capsaicin was administered to the rat paw to determine if the CB2 agonist reduced nociceptive pain and improved edema. Carrageenan is an inflammatory agent and in the first few hours following the injection, the reaction occurs in the two phases as the first phase in which the kinins, serotonin and histamine are released and the second phase in which the prostaglandins are released within 2-3 hours (23) Whereas capsaicin causes neurogenic inflammation in which vasodilatation, protein leakage and edema occurs by the release of vasoactive peptides such as neurokinin A, substance P and calcitonin gene-related peptide through the acute period (24,25).

GW405833 significantly decreased the plasma extravasations in both carrageenan-induced mix type inflammation and capsaicin-induced neurogenic inflammation of rat paw. In the previous study, paw thickness was found statistically significant in treatment carrageenan group at 1h, 2h, 3h and 4h, (6,25±0,147, 6,46±0,216, 6,64±0,243, respectively) (26). In the present study, as seen Table 1 and 2, paw thickness was found 5,87±0,25, 6,54±0,23, 7,24±0,13 and 7,71±0,23, respectively. These results are already supported in our previous study (16).

Table 1. According to time, change of paw thickness in the carrageenan-induced paw edema.

Treatment groups	According to time, change of paw thickness				
	0 h	1 h	2 h	3 h	4 h
Control	4,09±0,15	4,20±0,14	4,20±0,14	4,19±0,13	4,20±0,17
Car+Dic	4,50±0,14 ***	4,95±0,19 ***	5,19±0,10***	5,31±0,23***	5,37±0,12***
Car+CB2 Ago	4,26±0,14**	5,23±0,22**	5,46±0,16**	5,58±0,27**	5,63±0,13**
Car+CB2 Anta	4,45±0,12	5,55±0,15	6,24±0,32	6,58±0,27	6,95±0,33
Car+Vehicle	4,49±0,14	5,87±0,20	6,64±0,21	7,24±0,20	7,75±0,17
Car	4,34±0,15*	5,87±0,25*	6,54±0,23*	7,24±0,13*	7,71±0,23*
Car+CB2 Ago+Anta	4,25±0,17	5,47±0,15	5,89±0,25	6,23±0,24	6,49±0,25

Data are expressed as mean ± S.E.M. (n= 6) and one-way ANOVA followed by Tukey's multiple range test. Carrageenan treated lead to edema (*p< 0.001) as compared to Control group, pretreatment of CB2 agonist found statistically significant (**p < 0.05) as compared to Car group and diclofenac (***p < 0.05) inhibited carrageenan-induced paw edema as compared to Car group.

Table 2. According to time, percentage of change of paw thickness in the carrageenan-induced paw edema.

Treatment groups	According to time, % change of paw thickness			
	1 h	2 h	3 h	4 h
Control	2,80±1,09	2,72±0,73	2,45±0,84	2,84±0,78
Car+Dic	10,00± 1,41***	15,33± 2,42***	17,83± 3,19***	19,33± 2,73***
Car+CB2 Ago	16,05± 2,03**	21,33± 5,47**	24,00± 4,86**	25,00± 4,01**
Car+CB2 Anta	23,17±2,64	38,50±3,02	46,00±3,03	54,33±3,83
Car+Vehicle	30,33±1,86	47,50±1,05	60,67±0,82	72,17±4,17
Car	30,33±3,44*	45,33±3,61*	60,83±3,87*	71,17±2,48*
Car+CB2 Ago+Anta	21,50±1,05	30,67±1,75	38,33±1,63	44,01±1,79

Data are expressed as mean ± S.E.M. (n= 6) and one-way ANOVA followed by Tukey's multiple range test. Carrageenan treated lead to edema (*p< 0.001) as compared to Control group, pretreatment of CB2 agonist found statistically significant (**p < 0.05) as compared to Car group and diclofenac (***p < 0.05) inhibited carrageenan-induced paw edema as compared to Car group.

While administration of capsaicin was statistically significant when compared to salin group, treatment of GW405833 was significantly decreased edema when compared to capsaicin group (Table 3). In terms of% change of paw thickness according to 0 h; as seen Table 4, CB2 antagonist, Am630, prevented to the anti-inflammatory effect of CB2 agonist, GW405833. It was observed that the percentage of paw thickness decreased with the administration of CB2 agonist (Table 4).

Table 3. According to time, change of paw thickness in the capsaicin-induced paw edema.

Treatment groups	According to time, change of paw thickness				
	0 h	1 h	2 h	3 h	4 h
Control	3,89± 0,15	4,00 ±0,14	3,99± 0,14	3,98± 0,13	4,00 ±0,16
Car+Dic	4,50± 0,14*	5,23 ±0,22*	5,46 ±0,16*	5,58 ±0,27*	5,63 ±0,13*
Car+CB2 Ago	4,52 ±0,14**	4,95 ±0,19**	5,19 ±0,10**	5,31 ±0,23**	5,37 ±0,12**
Car+CB2 Anta	4,37 ±0,12	5,54 ±0,15	6,69 ±0,33	7,70 ±0,30	8,30 ±0,36
Car+ Vehicle	4,38 ±0,14	5,89 ±0,22	7,09 ±0,23	7,91 ±0,22	8,79 ±0,19
Car	4,59 ±0,15	5,81 ±0,21	6,99 ±0,24	7,92 ±0,14	8,61 ±0,25
Car+CB2 Ago+Anta	4,43 ±0,16***	5,40 ±0,13***	6,34 ±0,26***	6,91 ±0,27***	7,16 ±0,27***

Data are expressed as mean ± S.E.M. (n= 6) and one-way ANOVA followed by Tukey's multiple range test. Diclofenac inhibited plasma extravasation (*P<0.05), CB2 agonist significantly lead to inhibition of edema (**p< 0.001) as compared to Car group, CB2 antagonist (***p < 0.05) inhibited healing of CB2 agonist (***P < 0.001).

Table 4. According to time, percentage of change of paw thickness in the capsaicin-induced paw edema.

Treatment groups	According to time, % change of paw thickness			
	1 h	2 h	3 h	4 h
Control	2,81±1,07	2,73±0,72	2,47±0,83	2,83±0,76
Car+Dic	16,00±2,41	21,33±5,47	24,02±4,81	25,33±3,99
Car+CB2 Ago	10,05±1,04*	15,33±2,42*	17,83±3,19*	19,33±2,73*
Car+CB2 Anta	23,07±2,63	48,50±3,05	71,10±3,01	84,33±3,80
Car+ Vehicle	30,37±1,87	57,50±1,09	75,67±4,82	95,19±6,17
Car	30,48±3,44	55,61±3,61	75,84±3,71	91,74±4,48
Car+CB2 Ago+Anta	21,54±1,15**	40,55±1,71**	53,33±1,61**	59,01±3,91**

Data are expressed as mean ± S.E.M. (n= 6) and one-way ANOVA followed by Tukey's multiple range test. CB2 agonist strongly inhibited plasma extravasation in capsaicin-induced the neurogenic inflammation in paw tissue (*P<0.001). Diclofenac not inhibited plasma extravasation (P > 0.05). CB2 receptor antagonist significantly reversed the effect of CB2 agonist (**P<0,001).

The pretreatment with AM630 clearly reversed the effects of GW405833, which suggests a significant interaction between GW405833 and AM630. Thus, CB2 receptors mediate the anti-edematous and anti-plasma extravasations effects of GW405833. The present study increases the understanding that pharmacological level of CB2 agonist plays on anti-inflammatory effects by demonstrating that GW405833 reduces capsaicin or carrageenan-induced paw edema. These effects were similar in magnitude to those produced by

the CB2 agonist GW405833, as well as the nonselective COX inhibitor diclofenac (27). The anti-edematous effects of GW405833 were mediated through CB2 receptors. CB2 antagonist, AM630, reversed these anti-edema effects. These results suggest that the GW405833 reduces inflammation through the activation of CB2 receptors when administered after carrageenan, and that effect seems to be related to the suppression of neurogenic inflammation. The stimulation of CB2 receptors induces anti-inflammatory effects in several experimental conditions.

The other criteria for determining the extent of paw edema are measure paw thickness. In the previous study, administrate of carrageenan caused significantly edema in paw tissue (26). Consistent with previous findings, results of present investigation also showed that, in carrageenan-induced paw of rats, total protein content in paw tissue increased compared to the control group, whereas CB2 agonist administration reduced total protein content in paw tissue (28).

Our experimental studies provide evidence that supports the hypothesis for the activation of CB2 receptors may have beneficial effects against inflammatory processes, maybe via and related the control of neurogenic inflammation.

CONFLICT OF INTEREST:

The authors declare that there are no conflicts of interest.

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