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# The exogenous administration of CB2 specific agonist, GW405833, inhibits the inflammatory response by reducing cytokine production and oxidative stress

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# Our working team


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# Introduction

## Inflammation

- Inflammation is the body's response against invading pathogens,
- It is typically characterized by redness, swelling, pain, and heat.
- Several reports have provided evidence that inflammation is involved in the pathogenesis of many diseases including
  - aging,
  - cancer,
  - cardiovascular dysfunction,
  - other life-threatening and debilitating disorders.

# Introduction

## Inflammation

- Acute inflammation is a process that involved
  - the over production of free radicals
  - activation of a complex enzymes
  - release of several inflammatory or pro-inflammatory mediators

# Introduction

## Inflammation-Carregeenan model

- The carrageenan-induced paw edema is a well-known acute model of inflammation that is widely used for screening novel anti-inflammatory compounds

# Introduction

## Inflammation-Carregeenan model

- Carrageenan injection into the subplantar surface of rat paw induced a biphasic edema.
- The early phase observed around 1 h is related to the release of
  - Histamine
  - Serotonin
  - Bradykinin
  - to a less extent prostaglandins produced by cyclooxygenase enzymes (COX),

# Introduction

## Inflammation-Carregeenan model

- whereas the delayed phase is attributed to neutrophil infiltration and the continuing of the prostaglandin generation.

- Release of the neutrophil-derived
  - free radicals
  - nitric oxide (NO)
  - pro-inflammatory cytokines such as TNF-α and (IL-1β)

# Introduction

## Inflammation

- For this aim, when the agents;
  - carregenin,
  - formaline,
  - acetic acid,
  - prostaglandin,
  - histamine,
  - adenosine,
  - serotonin,
  - capsaisin etc

  are applied subcutoneously to the foot surfaces of the experimental animals, locally inflammation occurs at these tissues.

# Introduction

## Cannabinoid

- There are two well-known pathways of cannabinoid systems named CB1 and CB2 in the body.

- Latest researches point the possible important affects of cannabinoids on tissue inflammation and immunology.

- As experimental inflammation model, peripheral inflammation is be formed by using inflammatory agent and mediators on rat and/or mouse.

# Aim of This Research

- To prove the positive role of CB2 receptors
- To exhibit the affects of CB2 agonist and antagonist at inflammation
- To exhibit the unique mechanism of inflammation by means of CB2 receptors

To investigate the affects of CB2 agonist, antagonist and diclophenac on carregenan-induced paw oedema, by exogenous administered

# Materials and Methods

- Investigated parameters:

  - The serum cytokine levels (TNF-α and IL-1β)
  - The MPO activity, in paw tissue
  - MDA and GSH levels, in paw tissue
  - Histopathology

# Animals and Experimental Design

- The document was got from Local Ethic Committe.
- Experiments were performed at Kahramanmaraş Sütçü Imam University Laboratory Animals Department.
- In the study 200 - 270 gr Wistar albino rats were used.
- We used animals which consists of 7 groups (n=6-7).

# Materials and Methods

## Groups

- 1. Control
- 2. Carrageenan
- 3. Carrageenan + diclophenac
- 4. Carrageenan + CB2 agonist
- 5. Carrageenan + CB2 antagonist
- 6. Carrageenan + CB2 agonist + CB2 antagonist
- 7. Carrageenan + DMSO

# Materials and Methods

## Groups

- Group 1: Control (healthy): Just rigt back paw was given 0,1 ml saline

- Group 2: Carrageenan (Car): Just right back paw was given subcutoneously 0,1 ml 1 % w/v (10 ml saline including 100 mg carregeenan) carreegenan.
- Group 3: After Diclophenac Na (diclomec ampul, Abdi İbrahim İlaç Sanayii) was given at a dose of 10 mg/kg i.p., carregeenan was applied as above.

# Materials and Methods

## Groups

- Group IV: After 50 % DMSO (0,25 ml saline + 0,25 ml DMSO) at a dose of 3 mg/kg CB1 agonist, GW405833, was given i.v., carrageenan was applied as above.

- Group V: At a dose of 1 mg/kg CB2 antagonist, AM630, (dissolved at 50 % saline + DMSO) was given i.v. before carrageenan applying.

# Materials and Methods

## Groups

- Group VI: As the same dose above, CB2 antagonist and agonist were given i.v. respectively, then carragenan was applied.

- Group VII: Carrageenan + DMSO: After 0,5ml (50 % saline + DMSO) i.v. administration, carragenan was applied.

# Materials and Methods

- For biochemical analysis at hour 4, rats were anesthesized and blood samples were taken for biochemical analysis.
- According the KRC 30 11 TNF A alfa kite instruction, blood samples were centrifuged for 10 minutes at 4 centgrad degree with 2860 g. After centrifugation, blood samples were stored at -86 degree and then resolved for TNF alfa or IL-1beta.

# Materials and Methods

- Paw tissues that were taken for MPO, MDA and GSH were stored at -80 C
- Tissues were also placed 10 % formol solution for histopathological examination.

# Materials and Methods

## Statistical Data Analysis

- All statistical analyses were carried out using GraphPad statistical software.
- All data were presented as mean ± standard error deviation.
- Difference between groups was compared using One-Way ANOVA followed by Tukey's Multiple Comparison.
- $P < 0.05$ was considered significant.

# Results

- The administered of Carrageenan in paw tissue:
  - caused the decreased of tissue Glutathione (GSH) amount ($p<0.001$)
  - caused the increased of tissue Malondialdehyde (MDA) level ($p<0.001$)
  - caused the increased of tissue Myeloperoxidase (MPO) activity ($p<0.001$)

# Results

- caused the increased of serum Tumor Necrosis Factor (TNF-α) level ($p<0.001$)
- caused the increased of serum Interleukine (IL-1β) level ($p<0.001$)

# Results

- The systemic administered of CB2 agonist in carrageenan inflammation of paw tissue:
  - significantly returned the decreased of tissue GSH amount ($p<0.01$).
  - significantly inhibited the increased of tissue MDA level ($p<0.05$)
  - significantly inhibited the increased of tissue MPO activity ($p<0.01$)
  - significantly inhibited the increased of serum TNF-α level ($p<0.001$)
  - significantly inhibited the increased of serum IL-1β level ($p<0.01$)

# Results

- The systemic administered of diclophenoc, NSAID, in carrageenan inflammation of paw tissue
  - significantly returned the decreased of tissue GSH amount ($p<0.01$).
  - not changed the increased of tissue MDA level.
  - significantly inhibited the increased of tissue MPO activity ($p<0.01$).
  - not changed the increased of serum TNF-α and IL-1β levels.

**Figure 1. Effects of CB2 receptor agonist on GSH level in carrageenan-induced paw edema**

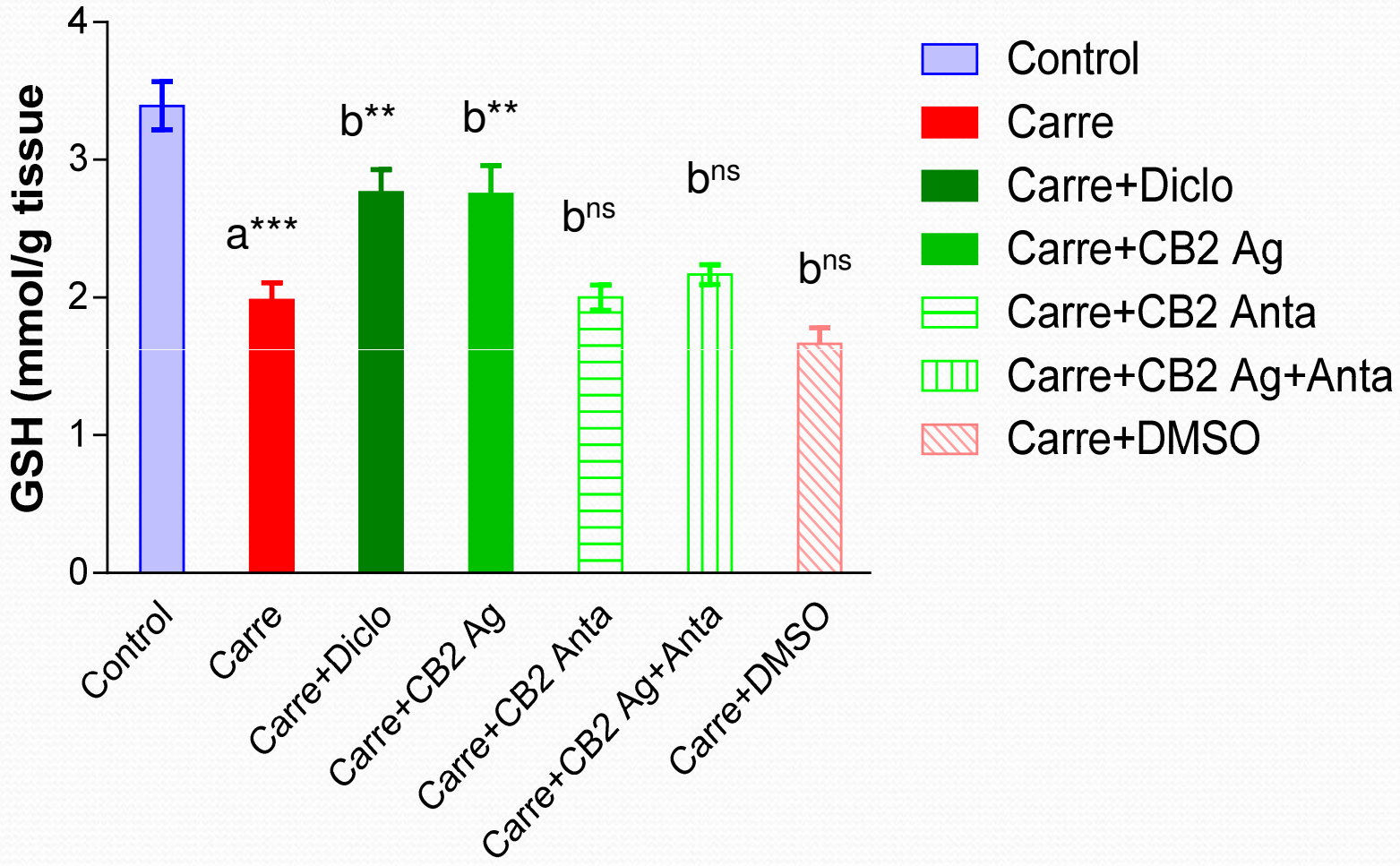


**Figure 2. Effects of CB2 receptor agonist on MDA activity in carrageenan-induced paw edema**

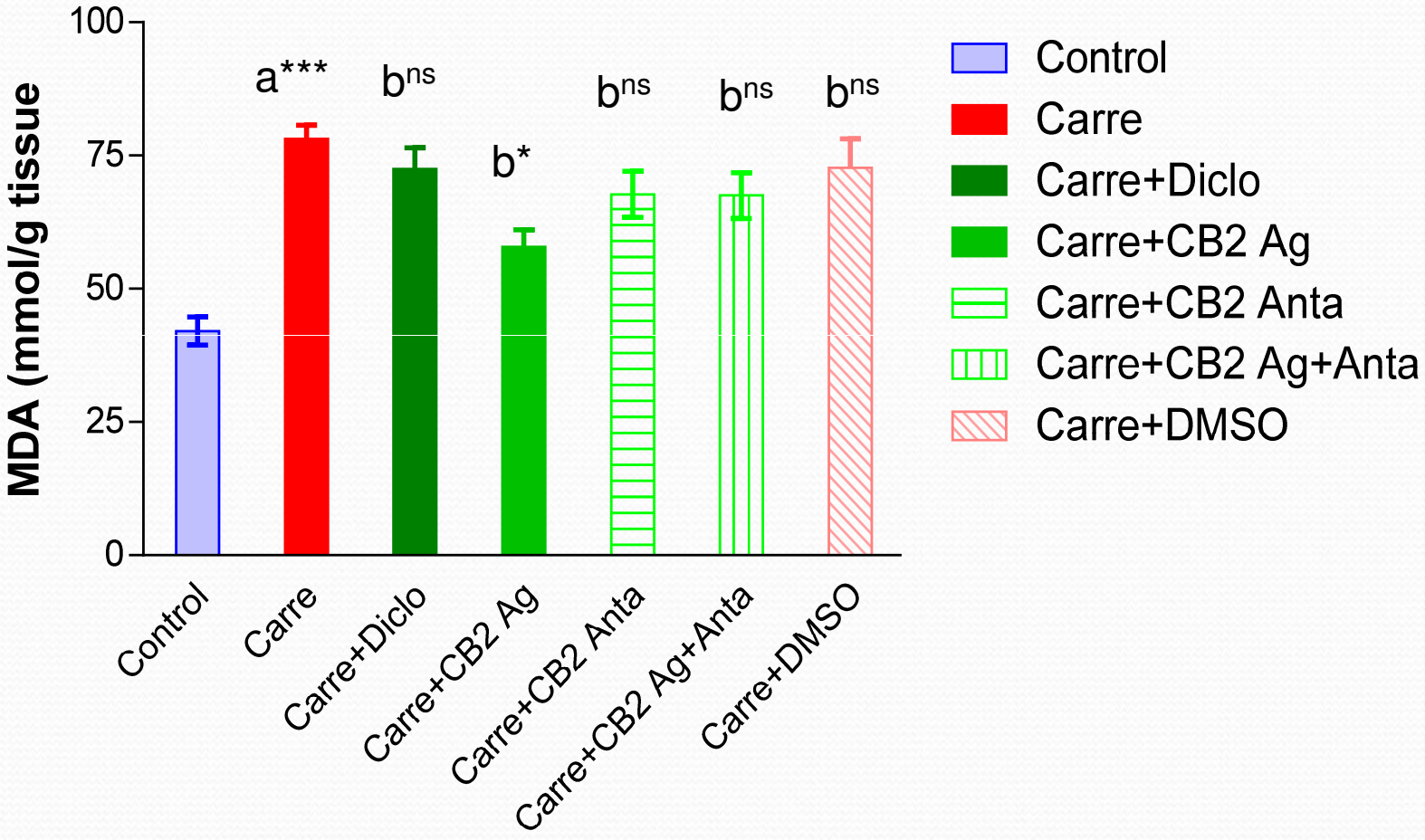


**Figure 3. Effects of CB2 receptor agonist on MPO activity in carrageenan-induced paw edema**

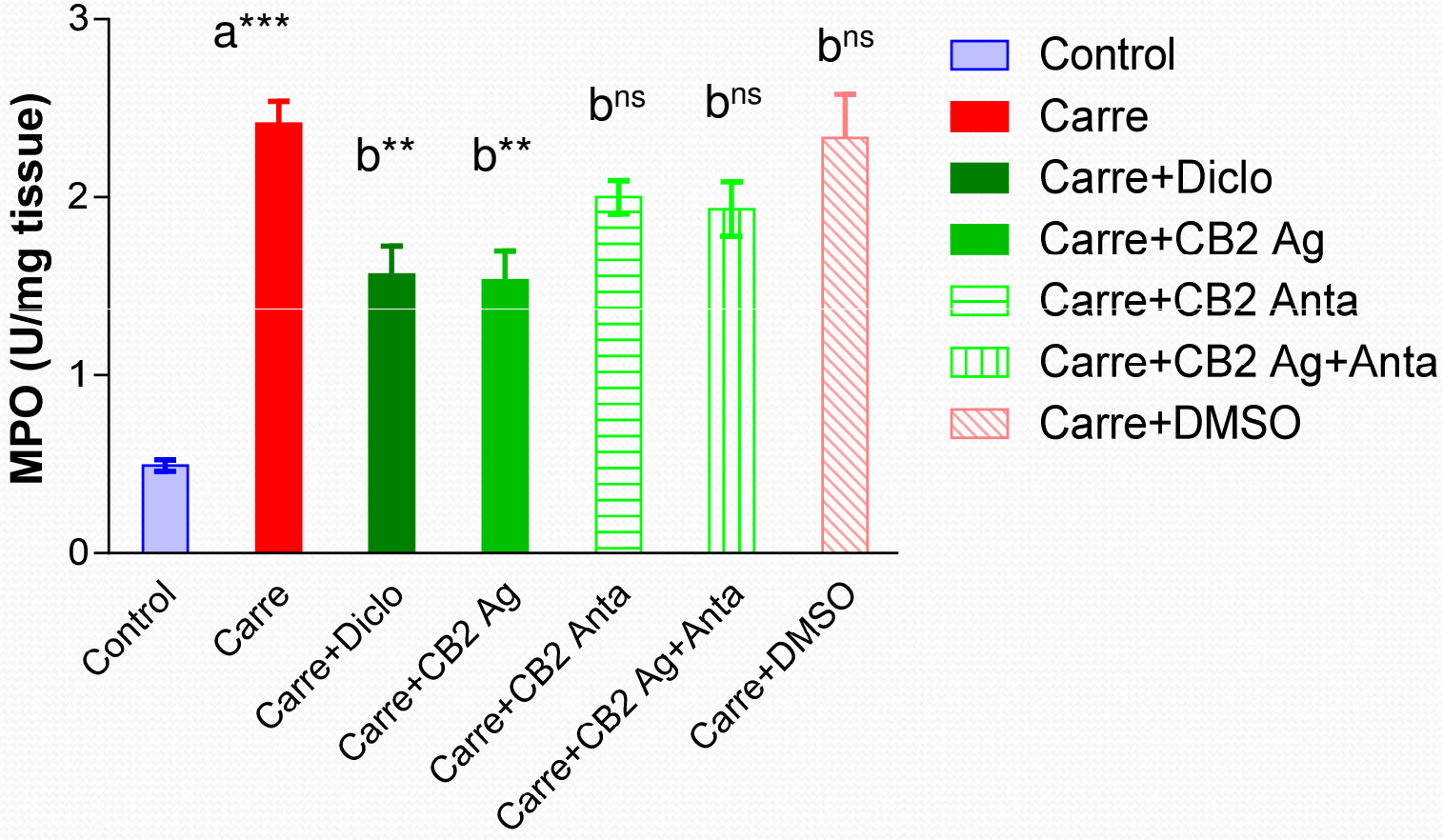


**Figure 4. Effects of CB2 receptor agonist on serum cytokines (TNF-α) in carrageenan-induced paw edema**

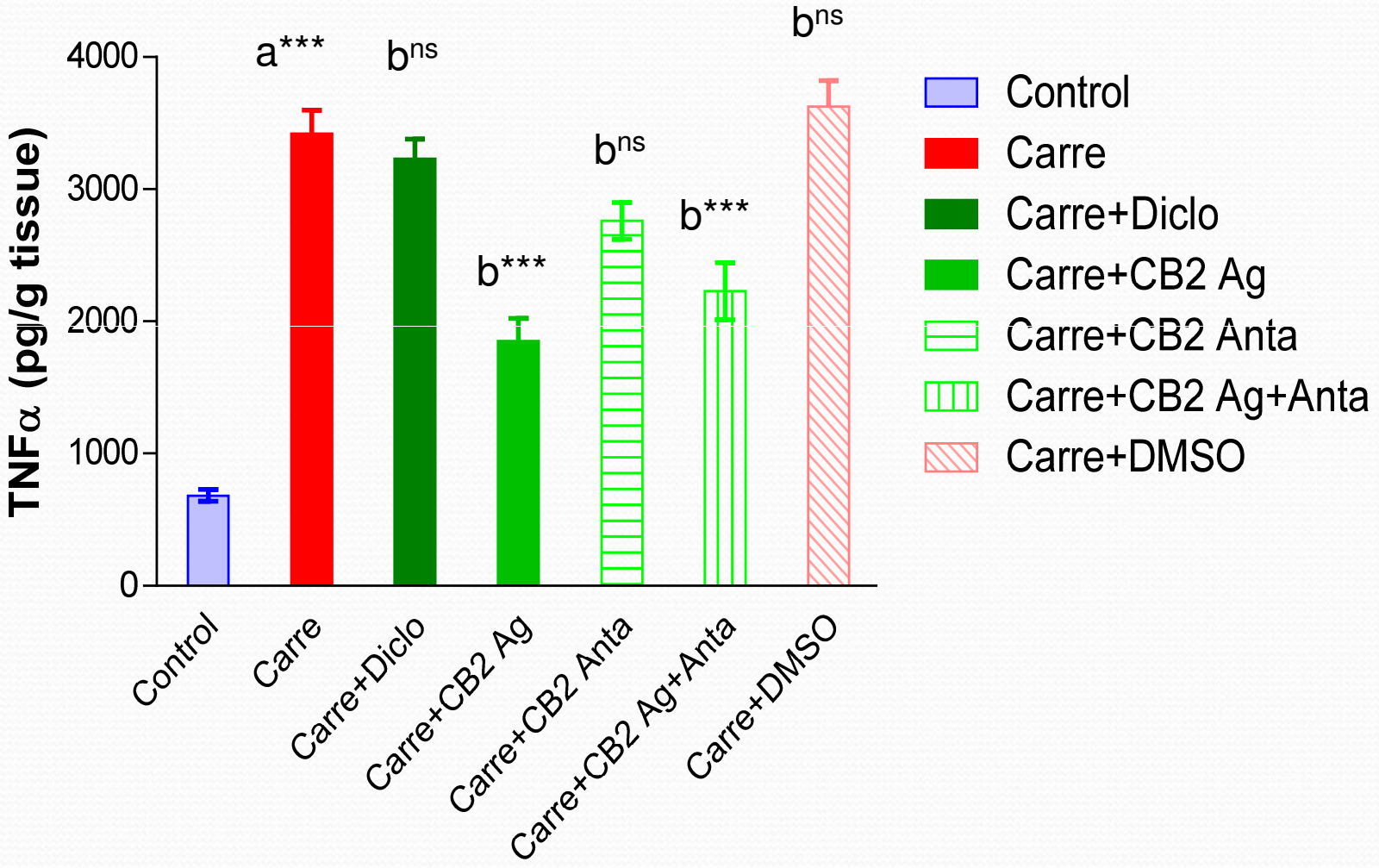
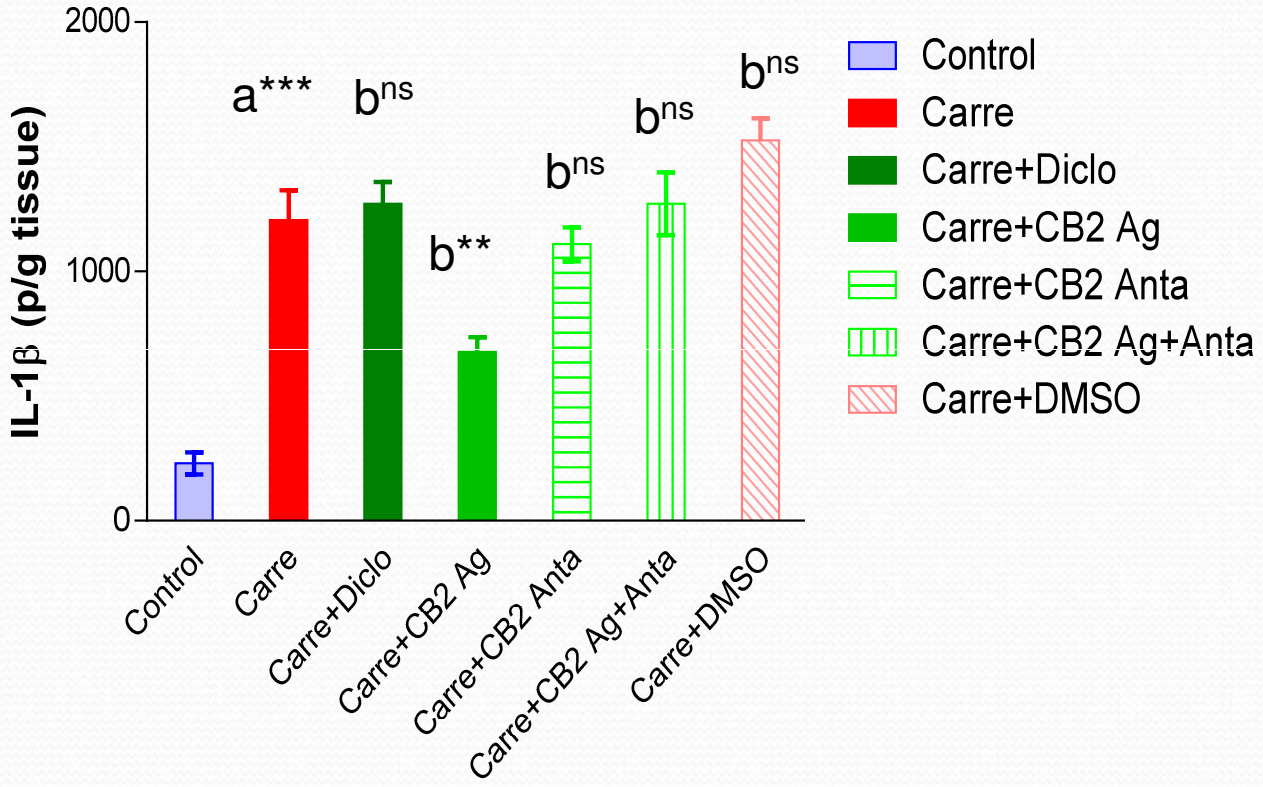


**Figure 5. Effects of CB2 receptor agonist on serum cytokines (IL-1β) in carrageenan-induced paw edema**



## Discussion

- The effects of cannabinoids on a variety of inflammatory processes and immune functions have been extensively reviewed, and it has been demonstrated that they may inhibit several enzymes that are activated in certain inflammatory conditions.

## Discussion

- The intraplantar injection of carrageenan is known to elicit an inflammatory response characterized by a time-dependent increase in paw edema, neutrophil infiltration and increased levels of inflammatory mediators in the paw exudate.
- The paw edema was maximal by the fourth hour following carrageenan administration

# Discussion

- In the present study, we showed that exogen administration of the cannabinoid 2 receptor agonist, GW405833, has an anti-inflammatory effect on carrageenan-induced rat paw edema and this anti-inflammatory potency was compared with that of the NSAID, diclophenac Na.

# Discussion

- The results indicate that this anti-inflammatory effect is due to suppression of oxidative stress, induction of the anti-inflammatory reduction in the proinflammatory cytokine TNF-alpha and IL-1beta release.

## Discussion

- In the present study, MDA was elevated, while GSH level was decreased during carrageenan-induced acute inflammation in rats.

- The results of this study demonstrated that CB2 agonist reduced paw MDA and restored the depleted GSH contents in the paw.

# Discussion

- TNF-a is a cytokine that plays a critical role in inflammation.
- It has been shown that TNF-a facilitates inflammatory cell infiltration by promoting the adhesion of neutrophils and lymphocytes to endothelial cells

# Discussion

- Several studies have reported that the ability of CB2 agonists to inhibit both cyclooxygenase and 5-lipoxygenase pathways of the arachidonate metabolism, as well as cytokine production may contribute to their anti-infammatory properties

# Discussion

- Results showed that cannabinoids significantly lowered inflammation.

- Accordingly, this study suggests that the reduction in oxidative stress and modulation of proinflammatory cytokines such as IL-1beta and TNF-a release by CB2 agonist may contribute to the anti-inflammatory effects.

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