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The Role of Aripiprazole (An Anti-psychotic Drug) in the Resolution of Acute Peripheral Inflammation in Male Wistar Rats

L. D. Adedayo[1*], D. A. Olawuyi[1], A. O. Ojo[1], O. Bamidele[1], S. A. Onasanwo[2] and A. O. Ayoka[1,3]

[1]Department of Physiology, Faculty of Basic and Medical Health Sciences, College of Health Sciences, Bowen University Iwo, Nigeria.
[2]Department of Physiology, Faculty of Basic Medical Sciences, College of Medicine, University of Ibadan, Ibadan, Nigeria.
[3]Department of Physiological Sciences, Faculty of Basic Medical Sciences, College of Health Sciences, Obafemi Awolowo University, Ile-Ife, Nigeria.

Authors' contributions

This work was carried out in collaboration between all the authors. Author LDA participated in the experimental design of the study, literature review, interpretation of the data and wrote the manuscript. Author DAO carried out the experimental procedures, participated in the literature review and data analysis. Authors AOA, OB and SAO participated in the literature review and data interpretation. Author AOO participated in the experimental design of the study, literature review and interpretation of the data. All authors read and approved the final manuscript.

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ABSTRACT

Aripiprazole, a known second generation anti-psychotic drug has been implicated to possess an anti-inflammatory potential, but yet not scientific adequately explored. This study investigated the role of aripiprazole in the resolution of acute peripheral inflammation in male wistar rats.

**Corresponding author: E-mail: delawbaba@gmail.com;*

Thirty six (36) male wistar rats were randomly divided into six groups. Group 1 was given orally 10 ml/kg normal saline while Group 2 received 0.1 ml of 1% carrageenan only at the right hind paw. Group 3 was given orally 0.1 mg/kg aripiprazole while Group 4 animals were administered by oral gavage 0.3 mg/kg aripiprazole. Group 5 was given orally 0.5 mg/kg of aripiprazole while Group 6 received 100 mg/kg aspirin. One hour after administration of either aripiprazole or aspirin, 0.1 ml of 1% carrageenan was injected into the right hind paw of all the groups except Group 1 which received 0.1 ml of normal saline at the right hind paw.
There was reduction in paw sizes of the animals given 0.5 mg/kg aripiprazole when compare with the control group (normal saline) at ($p<0.05$).
In conclusion, the study reveals that aripiprazole seems to have anti-inflammatory activities in carrageenan induced paw oedema in male wistar rats.

Keywords: Aripiprazole; anti-inflammation; carrageenan; anti-psychotic.

1. INTRODUCTION

Inflammation is a normal acute response of the immune system to pathogens and tissue injury [1]. The phenomenon of inflammation has become more important over the last few years, as its extensive involvement in more and more disorders is realized. Bronchial asthma was identified as an inflammatory disorder about 20 years ago, followed by various other allergies. Since then many others, such as diabetes type 1, Alzheimer's disease, various cancers, some heart diseases and even ageing have been identified as either acute or chronic inflammatory disorders [2].

The entire course of inflammation comes with many different processes involved in its initiation, regulation and resolution. Due to its extensive and widespread nature, inflammation is believed to have an impact on every aspect of normal human physiology and pathology [3].

There are several therapeutic approaches to the resolution of inflammation including steroidal and non-steroidal anti-inflammatory drugs (NSAIDs).

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used for the treatment of various types of inflammatory conditions. The pharmacological activity of NSAIDs relates to the suppression of prostaglandin biosynthesis from arachidonic acid by inhibiting the enzyme cyclooxygenases (COXs) and thromboxane synthase with a different degree of selectivity [4]. COX enzymes exist in two isoforms: COX-1 and COX-2 [5].

The COX-1enzyme is constitutively expressed in most tissues and the COX-2 enzyme is induced at sites of inflammation, pain and oncogenesis [6,7]. The therapeutic use of NSAIDs is associated with a broad spectrum of adverse reactions involving the liver, kidney, cardiovascular system, skin, and gut [8]. Gastrointestinal side effects are the most common and cover a wide clinical spectrum ranging from dyspepsia, heartburn, and abdominal discomfort to more serious events such as peptic ulcer with life-threatening complications of bleeding and perforation [9,10]. It has been reported that tinnitus, asthma, platelet aggregation and decrease sodium and fluid elimination resulting in edema accompanied NSAIDs intake [11]. The search for safer anti-inflammatory drugs with lesser side effects on long term usage is on the increase.

Antipsychotic drugs have been thought to possess an anti-inflammatory property by possibly decreasing the release of several inflammatory mediators or up-regulating omega-3-fatty acids biosynthesis which negatively regulates pro-inflammatory signaling cascades [12]. Antipsychotic medications are a class of psychiatric medications primarily used to manage psychosis (including delusions, hallucinations, paranoia or disordered thought), principally for schizophrenia and bipolar disorder, and there usage in the management of non-psychotic disorders is on the rise [13].

Aripiprazole (ARI) might be considered a "third-generation" antipsychotic agent and a relatively new antipsychotic that is differentiated from currently available atypical antipsychotics in its mechanism of action and adverse effect profile. Aripiprazole is a partial agonist at dopamine D2 receptors, a partial agonist at serotonin (5-HT) 1A receptors and an antagonist at 5-HT2A receptors [14] Also important for aripiprazole, is its neutral effect on bodyweight, triglyceride levels, prolactin levels and sedation [15]. However, the investigation into the anti-inflammatory effect of Aripiprazole in male wistar

rats has paucity of data. In view of this, this work was carried out to investigate the anti-inflammatory effect of Aripiprazole on male wistar rats.

2. MATERIALS AND METHODS

2.1 Chemical and Drugs

Carrageenan was purchased from S.D. Fine Chemical Pvt. Ltd. (Mumbai, India). Aripiprazole (10 mg) and Aspirin were purchased from Consilient Health Ltd Clonskeagh Dublin, Ireland.

2.2 Experimental Animals

A total of 36 male Wistar rats with weight range of 80-150 g purchased from the Laboratory Animal House of the College of Medicine University of Ibadan, Ibadan, Oyo state, Nigeria. The animals were kept in cages under standard conditions (temperature, 25±2℃, 12 hours light and 12 hours dark cycle) in the Animal House of the Physiology Department, Faculty of Basic medical Science, University of Ibadan, Ibadan, Oyo State, Nigeria. All animals were fed with commercially formulated rat feed and water ad libitum. After randomization into various groups, the rats were acclimatized for a period of 2 weeks in the environment before the initiation of the experiment. Their cages were cleaned of waste daily. The animals were fasted for 17 to 20 hours to prevent interference of food with drug intervention before experimentation. All procedures involving the use of animals in this study complied with the guiding principles for research involving animals as recommended by the declaration of Helsinki and the Guiding principles in the care and use of animals. The work is approved by the college of health sciences ethical committee Bowen University Iwo.

2.3 Experimental Design

Thirty six (36) male Wistar rats were distributed into six groups of six animals per group.

- **Group 1:** The control 1 received 0.1 ml normal saline by injecting into the right hind paw of the animals and 0.1 ml of 10 ml/kg normal saline was administered orally, without carrageenan injection and Aripiprazole administration.
- **Group 2:** The control 2 received 0.1 ml of 1% carrageenan by injecting into the right hind paw of the animals without Aripiprazole administration.
- **Group 3:** Animals in this group were administered orally with 0.1 mg/kg of Aripiprazole one hour prior injection of 0.1 ml of 1% carrageenan.
- **Group 4:** Animals in this group were administered by oral gavage with 0.3 mg/kg of Aripiprazole one hour before injection of 0.1 ml of 1% carrageenan.
- **Group 5:** Animals in this group were administered by oral gavage with 0.5 mg/kg of Aripiprazole one hour before injection of 0.1 ml of 1% carrageenan.
- **Group 6:** Animals in this group were administered orally with 0.5 ml of 100 mg/kg Aspirin (reference drug), one hour before injection of 0.1 ml of 1% carrageenan.

2.4 Anti-inflammatory Activity

2.4.1 Carrageenan-induced paw edema in rats

Carrageenan pedal acute inflammation was produced in the male Wistar rats according to [16]. An injection of 0.1 ml of 1% Carrageenan was delivered into the sub-plantar aponeurosis of the right hind paw of the rats.

The inflammation was quantified by measuring the volume displaced by the paw, using a plethysmometer (Ugo Basile) at time 0 and at 60 minutes interval for five (5) hours after carrageenan injection.

The inhibiting activity was calculated according to the following formula:

$$\% \text{ inhibition} = [(C_t - C_o) \text{ control} - (C_t - C_o) \text{ test}] / (C_t - C_o) \text{ control} \times 100$$

Where C_o = mean paw size in the control group at time zero and C_t = mean paw size in the treated group at time t.

2.5 Histological Studies

At the end of the experiment, the right hind paw (injected paw) of all animals in each group were excised after cervical dislocation, and fixed in 10% formalin. Tissue processing and staining using the Haematoxylin and Eosin (H&E) staining techniques were carried out at the department of histopathology (UCH) to check for degree of inflammation associated with morpho-logical changes in the paw of the experimental animals.

2.6 Statistical Analysis

All values are expressed as mean ± SEM. Data were analyzed by one-way analysis of variance followed by Newman-Keuls multiple comparison tests. Differences between means were considered significantly different when values of $p \leq 0.05$ were obtained using GraphPad Prism version 7.00 for Windows (GraphPad Software, San Diego, CA, USA; www.graphpad.com).

3. RESULTS

3.1 Effects of Aripriprazole on Carrageenan-induced Paw Edema in Male Wistar Rats

Inhibition of paw edema was least in the control groups. In the 0.1 mg/kg group, the paw sizes deceased after the third hour but was not statistically significant ($p<0.05$).

The paw sizes of the rats treated with 0.3 mg/kg of aripiprazole reduced slowly from the third hour to fifth hour and was statistically significant ($p<0.05$) when compared with the normal saline control group. At the fifth hour, the edema has completely disappeared in the group treated with 0.5 mg/kg of aripiprazole which was significant when compared with control (normal saline) group 1($p<0.001$).

The paw sizes of the rats treated with aspirin decreased progressively after second hour to the fifth hour and the sizes of the paw was restored after 5^{th} hour to the size of paw at zero hour approaching the basal level. In this group, the reduction in paw size was significant ($p<0.001$) when compared with the normal saline control group.

Inhibition against carrageenan-induced paw edema was dose dependent and greatest in 0.5 mg/kg group of aripiprazole with 100% inhibition.

Also, comparison between the normal saline control group with the carrageenan control group was statistically significant ($p<0.05$), supporting already established model by winter et al. 1962.

3.2 Histological Analysis

The infiltration of inflammatory cells was significantly decreased with treatment of aripiprazole (0.5 mg/kg) or aspirin (100 mg/kg) of body weight Fig. 1E and 1F.

4. DISCUSSION

The findings of the study revealed that Aripiprazole (ARI) exhibited some degree of anti-inflammatory effects. The anti-inflammatory property appears to be dose dependent. The animals in the group administered with 0.5 mg/kg ARI experienced rapid reduction in paw size against carrageenan-induced inflammation which was statistically significant. Also, the histological analysis displayed the evidence of anti-inflammatory potentials of Aripiprazole.

Carrageenan-induced inflammation is useful in detecting orally-administered, active anti-inflammatory agent, and to predict the value of anti-inflammatory agent acting by inhibiting the mediators of acute inflammation [17]. Paw edema induced by carrageenan is a biphasic event. The initial phase is attributed to the release of histamine and serotonin, whereas the second phase of edema is due to the release of prostaglandins, protease, and lysosome [18,19].

The animals administered with 0.3 mg/kg aripiprazole showed statistically significant decrease in paw size from the 3rd hour to the 5th hour after carrageenan-induced inflammation. However, the decrease observed during the 3rd to 5th hour in the animals treated with 0.1 mg/kg aripiprazole was not statistically significant.

Paw sizes was restored significantly to the zero hour levels at the 5th hour in 0.5 mg/kg group suggesting that the anti-inflammatory activity of aripiprazole at the dose of 0.5 mg/kg is more potent than aspirin at 100 mg/kg dose , a well-known NSAIDs. Though aspirin inhibition observed was found to reduce the paw size of animals at 5^{th} hour but the protection was lesser than 0.5 mg/kg aripiprazole showing anti-inflammatory activities offered by the anti-psychotic agent in this study.

The results obtained showed that aripiprazole at the highest dose 0.5 mg/kg possesses antagonistic potential which protects against the actions of inflammatory mediators such as histamine, serotonin produced in the early phase of the oedema as seen in the NSAIDs agent aspirin used as the reference drug in this study.

Table 1. Effects of graded doses of Aripiprazole on carrageenan-induced paw edema in male wistar rats at different hours (n=6)

Group / Treatment	Dose	Paw edema at zero hr (mL)	Paw edema at 1 hr (mL)	Paw edema at 2 hr (mL)	Paw edema at 3 hr (mL)	Paw edema at 4 hr (mL)	Paw edema at 5 hr (mL)	Change in paw size after 5 hr (mL)	% inhibition
Control 1 (Normal saline)	10 ml/kg	0.80±0.04$^{\beta c}$	0.83±0.08$^{\beta c}$	0.87±0.05$^{\beta c}$	0.83±0.08$^{\beta c}$	0.85±0.06$^{\beta c}$	0.89±0.05$^{\beta c}$	0.09±0.01	
Control 2 (Carragenaan)	0.1 ml of 1% Carr.	0.79±0.05	1.12±0.17	1.11±0.07	1.07±0.05	1.09±0.05	1 .06±0.06	0.27±0.01	
Aripriprazole	0.1 mg/kg	0.85±0.04	091±0.06	1.02±0.06	0.97±0.06	0.95±0.07	0.93±0.05	0.08±0.02	8.5%
Aripriprazole	0.3 mg/kg	0.88±0.02$^{\alpha c}$	1.01±0.06$^{\alpha c}$	1.13±0.04$^{\alpha c}$	1.07±0.08$^{\alpha c}$	1.01±0.05$^{\alpha c}$	0.92±0.04$^{\alpha c}$	0.04±0.02	18.3%
Aripriprazole	0.5 mg/kg	1.01±0.03$^{\alpha d}$	1.18±0.05$^{\alpha d}$	1.15±0.02$^{\alpha d}$	1.09±0.01$^{\alpha d}$	1.05±0.01$^{\alpha d}$	1.01±0.03$^{\alpha d}$	0.00±0.00	100%
Aspirin	100 mg/kg	0.92±0.07$^{\alpha d}$	1.35±0.13$^{\alpha d}$	1.11±0.09$^{\alpha d}$	0.98±0.07$^{\alpha d}$	0.93±0.08$^{\alpha d}$	0.91±0.08$^{\alpha d}$	-0.01±0.01	30.9%

$^{\alpha}$Comparison of mean values of rats administered aripiprazole or aspirin with control 1.
$^{\beta}$ Comparison of mean values between groups administered normal saline and 0.1% carragenaan.
Edema values are expressed as mean±SEM of six rats. $^{c}p<0.05$; $^{d}p<0.001$

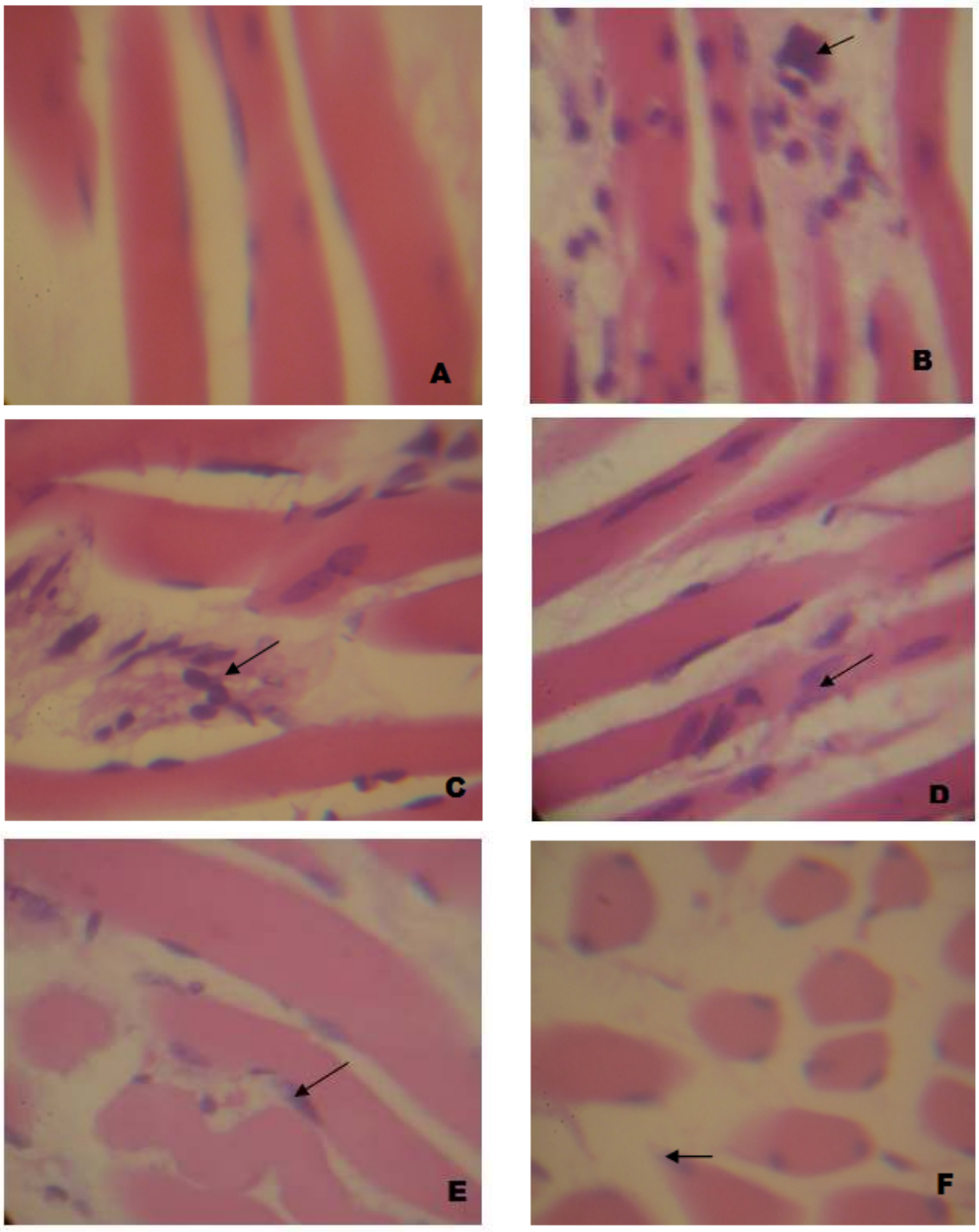

Fig. 1. Histological evaluation of anti-inflammatory effects of aripiprazole

Hematoxylin and Eosin staining of paw tissues of rats pre-treated with: (A) Normal saline 10 ml/kg, (B) 1% carr.,(C) 0.1 mg/kg aripiprazole +1% carr., (D) 0.3 mg/kg aripiprazole +1%carr., (E) 0.5 mg/kg aripiprazole +1%carr., (F) 100 mg/kg aspirin +1%carr., in the model of carrageenan-induced edema. Each photo is representative of six specimens for each group. All figures were magnified by 400X. Arrow indicates inflammatory cells in the treated group when compared with control

The second phase of oedema is sensitive to most clinically active anti-inflammatory drugs [20]. The ability of the anti-pyschotic drug (ARI) to completely inhibit oedema significantly in the late phase (5th hour) indicated that it may contain antagonistic property which were active against the liberation of prostaglandins and other inflammatory mediators usually released in the second phase of carrageenan-induced inflammation. Although, the mechanisms involved require laboratory experimental confirmation.

According to [17] agents that inhibit carrageenan-induced paw oedema significantly may have anti-inflammatory agents which act by inhibiting the mediators of acute inflammation. Therefore, the findings from this study are indications that atypical anti-pyschotic drug like aripiprazole (ARI) may be of potential benefit against inflammatory disorders.

Histological study indicated that carrageenan-induced inflammation is linked to intense edema characterized by increased migration of infiltrates inflammatory polymorphonuclear leukocytes (PMNs) cells, mainly neutrophils, in the inflamed paw tissues.

Our results are consistent with other carrageenan-induced inflammation animal model showing increased neutrophils migration to the site of injury [21,22,23]. Interestingly, Aripiprazole treatment drastically and dose-dependently diminished the inflammatory cell migration, most likely neutrophils, in carrageenan- induced rat paw edema. We also observed that the effect was similar to Aspirin, a well-known NSAID anti-inflammatory drug [24].

Thus, the present histological results in this study revealed that severe edema formation and elevated level of cellular infiltration in rats paw tissues decreased when treated with Aripiprazole (atypical antipsychotic drug) in a dose dependent manner. Hence, this study indicates that Aripriprazole (atypical antipsychotic drug) exhibited anti-inflammatory potential against carrageenan-induced paw edema in rats.

5. CONCLUSION

The results of this study revealed that Aripiprazole (atypical anti-psychotic drug) seems to possess anti-inflammatory potential by inhibiting carrageenan-induced inflammation in laboratory animals. This suggests that Aripiprazole could be a potential alternative therapy for the resolution of acute peripheral inflammation without associated adverse effects observed with NSAIDs. However, more research needs to be done on the mechanism(s) of anti-inflammatory activity of second generation anti-psychotic drugs such as Aripiprazole in experimental animals

CONSENT

It is not applicable.

ETHICAL APPROVAL

As per international standard or university standard, written approval of Ethics committee has been collected and preserved by the authors.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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