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Effect of Ropinirole in Experimentally Induced Colitis

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Abstract

Background: Ulcerative colitis is a chronic inflammatory disease that is linked with a large number of mortality and morbidity around the world. It causes inflammation in the colon's lining, leading to several symptoms that negatively affect the quality of life; no known cure is successful. As a result, it is imperative to investigate alternative treatment approaches. **Objectives:** This research aimed to assess the anti-inflammatory , anti molecular adhesion and macroscopic score impact of ropinirole on colitis in rat modules. **Materials and Methods:** Forty adult rats were grouped into four groups for this study. These groups included the control group, which was the negative control, the acetic acid group, which was the positive control; the acetic acid + sulfasalazine (100 mg/kg per day) group; and the acetic acid + or ropinirole 10mg/kg group. The rats were treated for one week. To induce colitis, 2 ml of acetic acid (4% (v/v) was installed inter-rectally. The animals were sacrificed, and the colonic tissue homogenate was analyzed for several markers. These markers included proinflammatory cytokines (TNF-α, IL-1β, NF κB), adhesive molecule markers (E-selectin, ICAM-1), and clinical parameters. **Results:** sulfasalazine and ropinirole pointedly compact the level TNF-α, IL-1β, and NFκB compared with the induced colitis. Colon homogenate of TNF-α and IL-1β did not differ significantly between groups 3 and 4; however, both treatment modalities significantly ameliorated the macroscopic score compared with induced colitis with the superiority of sulfasalazine or ropinirole. **Conclusions:** The results indicate that ropinirole is an effective treatment for induced colitis by reducing the inflammatory response and ameliorating clinical parameter.

Keywords: Ropinirole, Experimentally colitis, Disease Activity Index, Inflammatory, Macroscopical Score

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تأثير روبينيرول في التهاب القولون المستحث تجريبياً

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المستخلص

الخلفية: التهاب القولون التقرحي هو مرض التهابي مزمن يرتبط بعدد كبير من الوفيات والمرضية في جميع أنحاء العالم .يسبب التهاباً في بطانة القولون، مما يؤدي إلى ظهور عدة أعراض تؤثر سلباً على نوعية الحياة؛ لا يوجد علاج معروف ناجح .ونتيجة لذلك، لا بد من التحقيق في طرق العلاج البديلة .الأهداف: يهدف هذا البحث إلى تقييم التأثير المضاد للالتهابات والالتصاق الجزيئي والتأثير العياني للروبينيرول على التهاب القولون في الفئران .المواد والطرق: تم تقسيم أربعين فأراً بالغاً في أربع مجموعات لهذه الدراسة .وتضمنت هذه المجموعات مجموعة السيطرة والتي كانت السيطرة السلبية، ومجموعة حمض الأسيتيك والتي كانت السيطرة الإيجابية؛ مجموعة حمض الأسيتيك + سلفاسالازين (100 ملغم/كغم يومياً)؛ ومجموعة حمض الأسيتيك + أو روبينيرول 10 ملغم/كغم .تم علاج الفئران لمدة أسبوع واحد .للحث على التهاب القولون، تم تركيب 2 مل من حمض الأسيتيك (4٪ (حجم / حجم) عن طريق المستقيم . وتمت التضحية بالحيوانات، وتم تحليل تجانس الأنسجة القولونية لعدة علامات. وشملت هذه العلامات السيتوكينات المسببة للالتهابات-TNF) α، IL-1β)، (NF κB، علامات جزيء لاصق(E-selectin) ، ICAM-1 . النتائج: اظهر كل من علاج السلفاسالازين والروبينيرول تاثيرا واضحا في تقليل مستويات TNF-α، IL-1β، و NFκBمقارنة مع التهاب القولون المستحث .لم يختلف متجانس TNF-α و IL-1β بشكل كبير بين المجموعتين 3 و 4؛ ومع ذلك، فإن كلا من طرق العلاج حسنت بشكل كبير النتيجة العيانية مقارنة مع التهاب القولون المستحث مقارنه

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معلومات البحث
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مع السلفاسالازين أو الروبينيرول.الاستنتاجات: تشير النتائج إلى أن عقار الروبينيرول ممكن استخدامه علاج لالتهاب القولون المستحث لما له من تاثير عن طريق تقليل الاستجابة الالتهابية وتحسين العلامات السريرية .

الكلمات المفتاحية : روبينيرول، التهاب القولون التجريبي،مؤشر نشاط المرض، الالتهابات، النتيجة العيانية

Introduction Ulcerative colitis is a chronic disease related to areas from immunity disorder characterized mainly by GIT (gastric intestinal tract). The symptoms can include diarrhoea, abdominal pain, and fatigue, leading to malnutrition and weight loss [1]). Furthermore, the symptoms can affect the mental health and social functioning of individuals. Therefore, the symptoms of ulcerative colitis can significantly impact the quality of life. The etiology of the disease remains unknown, although it is involved in irregular inflammation of antigens, either internal, microorganism, or environmental origins, resulting in the propagation and increase of this inflammation [2] [3]. Several studies observed abnormal inflammatory responses in several locations of the colon with an increase in the number of White blood cells and T lymphocytes, mast cells, and other types of inflammatory cells that released their inflammatory mediators after activation [3]. The activation of these cells increases the secretion of various proinflammatory cytokines and chemotactic substances in improper amounts, which will cause damage to the surrounding tissues and the spread of inflammatory comeback. There are several types of inflammatory cytokines which are associated with Ulcerative colitis, such as tumour necrosis factor-alpha (TNF-α) and interleukin-1 beta (IL-1β) [4]. It is imperative to note that early treatment can improve outcomes and prevent complications. Treatment can reduce the severity and frequency of symptoms, leading to improved quality of life. Additionally, treatment can prevent or delay the need for surgery, which is often associated with complications. Moreover, early treatment can decrease the hazard of a colon tumour, a severe complication of ulcerative colitis. Therefore, early treatment is crucial in managing ulcerative colitis. Although significant progress has been complete in the conduct of ulcerative colitis, drug-induced toxicity over extended treatment.

The periods and the high relapse rate limit the application of established treatments. Therefore, novel strategies for restoring the altered immune response are needed [5]. Ropinirole is a pharmacological agent that exhibits selectivity towards the dopamine D2-like receptor agonist, belonging to the non-ergoline class of compounds. It has a notable affinity for the D2, D3, and D4 receptor subtypes. Ropinirole HCl displays minimal binding affinity for dopamine D1 receptors while demonstrating modest functional efficacy towards 5-HT2 receptors [6]. As per Cochen De Cock's [7] findings, these pharmaceuticals are administered to address the symptoms of Parkinson's disease and the primary restless legs syndrome of moderate to severe intensity. Therefore, the aim of study is to investigate the potential anti-inflammatory and anti-molecular adhesion effect in experimentally induced colitis.

Materials and Methods

Experimental animals

In our research, adult male albino rats weighing (200–220 g) were employed. The rats were housed in polypropylene clean cages in a relatively stable

condition, with a temperature of about 24–25 degrees Celsius, a humidity of 35–60 per cent and a (12/12 h day to night cycle). We stopped rat feeding for about 24 h prior to the induction of colitis to ensure deprivation and complete induction of colitis, but they received water only. The rats were housed in enclosures featuring broad wire-mesh flooring as a preventative measure against coprophagy. Prior to colitis induction, the subjects were instructed to withhold water for two hours [8]. This study was experimental controlled animal study that has been conducted in the Department of Pharmacology in College of Medicine, between December 2021 and May 2023. All the experimental studies were carried out under the supervision of protocol approved by Al-Nahrain University of Medicine. Institutional Review Board (IRB)committee Approval Number (20210903 and 21.NOV .2021).

Induction of ulcerative colitis

The rats underwent a fasting period of no less than 24 h prior to the induction of colitis. This procedure was performed to ensure proper installation by clearing the colon of faecal matter. Nevertheless, the rats had free access to tap water during this period. The induction of colonic ulceration was conducted experimentally with a modified version of the procedure recommended by Mousavizadeh et al., [9]. In this study, the rats were administered a single intrarectal infusion of a 4% acetic acid solution at a dose of 5 ml/kg for a duration of 30 s. The infusion was delivered 8 cm into the colon with a flexible plastic tube while the rats underwent light ether anesthesia (2 mm outside diameter). The release of acetic acid was inhibited by positioning the rats horizontally for 2 min.

Experimental design

The experiments were divided into four categories (ten rats for each group). Group I was non-treated and served as the negative control (normal saline infusion through the rectal route). In the other groups, rectal administration of (4%) acetic acid (v/v) induced colitis. Group II represented positive control and received normal saline orally, group III was treated orally with sulfasalazine (100 mg/kg/day), and Group IV was treated orally with ropinirole (10 mg/kg/day). In all groups, treatment lasted for seven days. The duration of the treatment was determined according to prior studies on experimental colitis [10].

Preparation of Drugs

Sulfasalazine and ropinirole were prepared before administration. As suspensions in the distilled water, drugs were prepared. The recommended dosage of Sulfasalazine was 100 mg/kg.

Tissue Samples

Upon the completion of the experiment, the rats were euthanized with an excessive dose of diethyl ether. The colon was expeditiously excised subsequent to abdominal dissection. A longitudinal incision was made on the colon, delicately irrigated with normal saline. Colon samples were collected, rinsed with PBS (0.02 mol/L; pH 7.2–7.4) and weighed at a keep at a temperature of -80 °C. The tissue samples were sliced into small fragments and subsequently homogenized in a specified quantity of PBS (1 g of tissue in 9 ml of PBS) with a homogenizer; subsequently, the homogenate was subjected to centrifugation at a rate of 5000 commotions perminute for 15 min. The levels TNF-α, IL-1β and NF-κB (inflammatory cytokines); and ICAM-1 and E–

selectin (adhesion molecules) in the homogenized colon tissues were measured by ELISA kits as following the manufacturer's instructions (Elk Biotechnology -Chania).

Macroscopic evaluation

Disease activity index (DAI)

The Disease Activity Index (DAI), defined by Niu et al. [11], was employed to assess the disease clinically. This index included evaluating body weight reduction, stool consistency, and rectal bleeding. Scores were assigned as follows: body weight reduction was categorized into five grades: (0) no reduction or weight gain, (1) 1-5% reduction, (2) 6-10% reduction, (3) 11-20% reduction, and (4) more than 20% reduction. Stool consistency was graded into three categories: (0) normal, (2) loose, and (4) diarrhea. Rectal bleeding was also divided into three grades: (0) normal, (2) mild, and (4) severe bleeding. The total DAI score was calculated as the sum of the scores for body weight reduction, stool consistency, and rectal bleeding. The presence of blood in the stool was determined using the benzidine test. Well-formed pellets were considered normal stool, pasty stools that did not stick to the anus were classified as loose stool, and liquid stool that sticks to the anus was categorized as diarrhea.

Colon edema

Colon edema was used as an indicator of tissue edema and colitis severity. The colon specimens obtained from each animal were excised along the mesenteric border and subsequently rinsed with care. The presence of oedema was ascertained by employing an overly sensitive balance to measure the weight of an 8 cm segment of the colon. Prior to weighing, the tissue was subjected to blotting on a filter paper to eliminate any superfluous water [12].

Macroscopic colonic score

The determination of the macroscopic colonic score was carried out through visual assessment, utilizing the scoring system outlined by Appleyard and Wallace [13], which is as follows: Scores are allocated according to the clinical characteristics of the colon, utilising a five-point scale that ranges from 0 to 4, as outlined below: There was no observable change at a macroscopic level. The grading system for mucosal inflammation includes four levels: level 1, characterised by mucosal erythema alone; level 2, which involves slight mucosal oedema and small erosion; level 3, where moderate oedema, bleeding ulcers or erosion are present; and level 4, which is characterised by severe ulceration, erosions, oedema, and tissue necrosis.

Statistical Analysis

The data were presented as mean values accompanied by their respective standard deviations. The comparison of means between the two groups was carried out using an unpaired t-test. In contrast, the comparison of means among five drug groups was conducted using ANOVA (analysis of variance) with the post hoc Tukey test. The Statistical Package for Social Sciences (SPSS) version 24 was utilised for conducting the data analysis. The statistical significance was established based on a p-value that was lower than 0.05.

Results

Tissue level homogenate of NF-κB and TNF-α, IL-1β were significantly increased in the colitis group

(434.5 ± 53.47 **pg/ml**, 646.1 ± 58.65 **pg/ml** and 9.05 ± 0.74 **pg/ml**, respectively) as compared with the healthy control group (139.8 ± 76.57 **pg/ml**, 142.5 ± 42.09 **pg/ml** and 1.21 ± 0.75 **pg/ml**, respectively). The Ropiniorole had statistically significantly reduced the levels of TNF-α (248.26±100.97 pg/ml), IL-1β (286.22±59.71 pg/ml) and NF-κB (4.02 ±1.01 **pg**/ml) compared to Sulfasalazine (197.25 ± 64.97 **pg/ml**,190.87 ± 36.86 **pg/ml** and 2.11 ± 0.88 **pg/ml**, respectively), as shown in Table 1).

Table 1: Proinflammatory cytokines of tissue-level homogenates in different groups, adhesion molecules

Variables	Healthy control (n = 10)	Induced colitis (n = 10)	Sulfasalazine (n = 10)	Ropinirole (n = 10)	P value
Colonic TNF-α pg./ml	139.8 ± 76.57 A	434.5 ± 53.47 B	197.25 ± 64.97 C	248.26±100.97 D	**<0.001**
Colonic IL-1β pg/ml	142.5 ± 42.09 A	646.1 ± 58.65 B	190.87 ± 36.86 C	286.22±59.71 C	**<0.001**
Colonic NF-κB pg/ml	1.21 ± 0.75 A	9.05 ± 0.74 B	2.11 ± 0.88 C	4.02 ±1.01 D	**<0.001**

TNF- tumour necrosis factor alpha; IL-1 interleukin 1-beta; and NF--κB nuclear factor-kappa beta. The data were presented in terms of mean values standard deviations (SD). Different letters indicate significant differences**.**

As displayed in (Table 2), the levels of E-selectin and ICAM-1 were elevated after induction by acetic acid (7.43 ± 0.53 **ng/ml** and 432.5 ± 71.3 **pg/ml**, respectively) in comparison with those in the healthy control group (1.33 ± 0.58 **ng/ml** and 165.70 ± 65.12 **pg./ml**, respectively). However, the Ropinirole reducing ICAM-1 and E-selectin (3.42 ± 0.72**ng/ml** and 308.20 ± 49.82 **ng/ml**, respectively) compared with those in the induction control group.

Table 2: Adhesion molecules of tissue-level homogenates in different groups. Different letters indicate significant differences

Variables	Healthy control (n = 10)	Induced colitis (n = 10)	Sulfasalazine (n = 10)	Ropinirole (n = 10)	P value
Colonic ICAM ng/ml	1.33 ± 0.58 A	7.43 ± 0.53 B	2.01 ± 0.67 A	3.42±0.72 C	**<0.001**
Colonic E-selectin pg./ml	165.70 ± 65.12 A	432.5 ± 71.3 B	194.37 ± 50.60 C	308.20±49.82 D	**<0.001**

ICAM-1, intercellular adhesion molecule-1; E-selectin, endothelial selectin. Values were expressed as mean ± SD.

At the same time, multiple comparisons of the Disease activity index and Macroscopic in different groups are shown in Table 3. For DAI, all treated groups had lower DAI than the induced colitis group, with significant differences. Ropinirole-treated group had the highest score (3.50±1.05), with a significant difference from all other groups. Macroscopic score all treated groups had MAC than the induced colitis group with substantial differences. The Ropinirole-treated group had the (2.17±0.75), while all differed significantly from Induced colitis. All treated groups differed significantly for Induced colitis in CW but did not differ significantly from each other's, while all differed significantly from induced colitis.

Table 3: Multiple comparisons of disease activity index, m acroscopic (clinical parameter):

Variables	Healthy control (n = 10)	Induced colitis (n = 10)	Sulfasalazine (n = 10)	Ropinirole (n=10)	P value
DAI	0.00±0.00 A	11.0±0.89 B	1.17±0.41 C	3.50±1.05 E	**<0.001**
MAC	0.0±0.00 A	5.67±0.52 B	1.83±0.41 C	2.17±0.75 C	**<0.001**
CW(g)	1.53±0.28 A	3.27±0.93 B	1.43±0.14 A	1.68±0.28 A	**<0.001**

DAI: Disease Activity Index; MACScore: Macroscopical Score; CW: colon weight; Different letters indicate significant differences; similar letters indicate insignificant differences. pvalues expressed as mean ± Standard deviation (SD). n= number of animals.

Discussion

A common healthcare problem concerning people of all ages is UC. The present UC treatment has a number of side effects and loses effectiveness with time, prompting the use of alternate and more potent medicines [14]. In the study, colon weight was contrarywise correlated to the severity of colon inflammation. The findings of the investigation suggest that rats with acetic acid-induced colitis experienced a notable elevation in their DAI score and an augmentation in colon weight. The present study has identified an augmented colon size as a result of pronounced oedema, necrosis, and infiltration of inflammatory cells [15]. These results are comparable with the findings of preceding studies that have been exposed that Ropinirole has a neuroprotective action and anti-inflammatory effect, reduces oxidative stress, and is involved in the protection of dopaminergic neurons [16]. A further study proposed that inflammatory cytokines released from the activated immune cells found in the brain of Parkison disease patients may induce apoptosis directly through TNF-alpha cell surface receptors, and ropinirole blocks this effect [17]. Furthermore, D2-agonist markedly decreases intracellular nitric oxide formation, expression of pro-inflammatory genes, TNF-alpha, and IL-6, which reflects reduced pro-inflammatory responses [18], in another related study presented by Tolstanova et al. [19] which had approved that taking dopaminergic agonist associated inhibition of NFκB. The current investigation revealed that Ropinirole induced a noteworthy decrease in the tissue homogenate of adhesion molecules (E selectin) and ICAM-1 in the colonic mucosa of rats compared to the colitis group that did not receive treatment. Numerous studies have indicated that the activation of NF-κB may play a pivotal role as a fundamental factor in the pathophysiology of chronic inflammation in the intestine. The up-regulation of proinflammatory molecules, such as TNF-1 and ICAM-1, through the activation of NF-κB has been observed to play a role in the onset and progression of TNBS-induced colitis, as reported by Li et al. [20]. The administration of Ropinirole at a dosage of (10 mg/kg/day) resulted in a significant reduction in the mean DAI score and gross amelioration in colitis. This observation was further corroborated by evidence of macroscopic improvement, as indicated by a reduction in colon weight in rats with colitis. This finding aligns with the results of Lee et al. [21], who demonstrated that the administration of dopaminergic agonists was linked to a reduction in colonic weight in rats with experimentally induced colitis. On the hand, several studies have shown that Cabergoline (dopamine agonist) reduced weight loss, a lower DAI score, associated with less histopathological findings, and lower serum levels of the cytokines TNF-α, IL-6, and CCL2 [22] [19] . Ropinirole is a dopamine D2-like receptor agonist that exhibits selectivity towards non-ergoline receptors. It has a notable affinity for the D2, D3, and D4 receptor subtypes [21]. According to Liu et al. [23], the administration of medication is recommended for the management of both the manifestations of Parkinson's disease and moderate-to-severe Restless Legs Syndrome. The available evidence suggests that there exists a reciprocal relationship between inflammation in the gastrointestinal tract and neurodegenerative processes, which is consistent with the notion of the 'gut-brain axis'. Furthermore, recent population-based research has indicated that the presence of inflammatory bowel disease may

increase the risk of developing Parkinson's disease. Thus, Ropinirole could ameliorate and reduce the UC through the 'gut-brain axis'; besides, it may have an anti-inflammatory and antimoleculer effect [24] [25].

Conclusion

The therapeutic impact of ropinirole on ulcerative colitis is suggested by the results. It could, in part, be because of its anti-inflammatory and anti-adhesion molecular properties when compared to sulfasalazine in experimentally induced colitis.

Recommendations

1. Further Experimental studies are needed to explore other possible mechanisms for investigated drugs(Ezetimibe and Ropinirole (e.g.: Toll-like receptor)
2. Experimental studies on animal models are recommended to test The anti-inflammatory effect of tested drugs (Ezetimibe and Ropinirole and a combination of Sulfasalazine +Ezetimibe) in other inflammatory-related diseases. (e.g.: Chron's disease)
3. Experimental studies are recommended to test other members of drugs within the same classes on acetic acid-induced colitis in rats.
4. It is recommended to test other doses, other routes of administration,and other periods of treatment for investigated drugs on acetic acid-induced colitis in rats.

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Ethics.

This study, which used a cross-sectional approach, was conducted in compliance with a protocol that was reviewed by the institutional review board at Al-Nahrain University's College of Medicine. The scientific committee of the pharmacology department at the same university approved this review.

Author contributions F.R. J.; draft writing, condecting all research, submition the article; A. A revision and help in condecting all research.

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