Central Asian Research Journal For Interdisciplinary Studies (CARJIS). ISSN (online): 2181-2454
Volume 4 | Symposium Special Issue |November, 2025 | SJIF: 5,965 | UIF: 7,6 | ISRA: JIF 1.947 | Google Scholar | https://carjis.afu.uz/

УДК:616.33:615.014.3:577.1

# THE EFFECTS OF DOPAMINE RECEPTOR AGONISTS ON THE COURSE OF ASEPTIC IN-FLAMMATION INFLAMMATION

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**ABSTRACT**

In experimental studies, the effect of levodopa and bromocriptine compared with sodium diclofenac on the features of the course of aseptic inflammation induced by dextran, histamine and carrageenan was studied. It was found that the studied dopamine mimetics clearly suppress the exudation process when exposed to flagogens of various mechanisms of action. It is believed that the mechanism of the antiexudative action of dopamine receptor agonists is largely due to their peripheral adrenomimetic effect, leading to vasoconstriction. In a separate series of experiments using the "cotton wool granuloma" technique, the antiproliferative property of dopamine receptor agonists was proven. It was concluded that in terms of increasing the effectiveness of pharmacotherapy, the use of dopamine mimetics in medical practice should be carried out taking into account their antiexudative and antiproliferative properties.

**Key words:** dopamine mimetics, aseptic inflammation, dextran, histamine, carrageenan, proliferation.

**ANNOTATSIYA**

Eksperimental tadqiqotlarda levodopa va bromokriptinning diklofenak natriy bilan solishtirilgan holda dekstran, gistamin va karragenan orqali chaqirilgan aseptik yallig‘lanishning kechish xususiyatlariga ta’siri o‘rganildi. O‘rganilgan dofamin mimetiklari turli ta’sir mexanizmlariga ega flagogenlar ta’sirida ekssudatsiya jarayonini aniq ravishda susaytirishi aniqlangan. Dofamin retseptorlari agonistlarining antiekssudativ ta’sir mexanizmi asosan ularning periferik adrenomimetik ta’siri, ya’ni qon tomirlarning torayishi (vazokonstriksiya) bilan bog‘liq deb hisoblanadi. Alohida tajriba seriyasida “paxta granulomasi” modeli yordamida dofamin retseptorlari agonistlarining antiproliferativ xususiyati ham isbotlandi. Xulosa qilinishicha, farmakoterapiya samaradorligini oshirish nuqtai nazaridan dofamin mimetiklarini tibbiyot amaliyotida qo‘llashda ularning antiekssudativ va antiproliferativ xususiyatlarini inobatga olish zarur.

**Kalit so‘zlar:** dofamin mimetiklari, aseptik yallig‘lanish, dekstran, gistamin, karragenan, proliferatsiya.

**АННОТАЦИЯ**

В экспериментальных исследованиях изучено влияние леводопы и бромокриптина в сравнении с диклофенаком натрия на особенности течения асептического воспаления, вызванного декстраном, гистамином и карагенином. Было установлено, что исследуемые дофаминомиметики чётко подавляют процесс экссудации при воздействии флогогенов различного механизма действия. Считается, что механизм антиэкссудативного действия агонистов дофаминовых ре-

цепторов в значительной степени обусловлен их периферическим адреномиметическим эффектом, приводящим к вазоконстрикции (сужению сосудов). В отдельной серии экспериментов с использованием метода «ватной гранулёмы» было доказано антипролиферативное свойство агонистов дофаминовых рецепторов. Сделан вывод, что для повышения эффективности фармакотерапии применение дофаминомиметиков в медицинской практике должно осуществляться с учётом их антиэкссудативных и антипролиферативных свойств.
**Ключевые слова:** дофаминомиметики, асептическое воспаление, декстран, гистамин, каррагенин, пролиферация.

## INTRODUCTION

The autonomic nervous system can exert a modulating effect on the activity of internal organs using the same mediators. The modulating effect consists in strengthening or weakening the intensity of organ functioning. Such an effect is carried out, firstly, using electrophysiological processes, and secondly, by triggering biochemical reactions by means of secondary mediators. It should be taken into account that changes in the ratio of sympathetic and parasympathetic nervous system activity can, in some cases, serve as a trigger for the development of various inflammatory pathologies. While the influence of these systems on inflammatory processes has been extensively studied, the role of the dopaminergic system in this context remains insufficiently explored. Neuroinflammation plays a crucial role in the pathogenesis of Parkinson's disease. In this regard, it seems important to study the modeling effect of drugs used to treat this pathology and extrapyramidal disorders. Due to the development of severe complications with untimely detection and treatment of diseases, in the basis of the pathogenesis of which the inflammatory process plays a decisive role, they are classified as socially conditioned, affecting a significant part of society. In this regard, the establishment of the role of various endogenous, and especially neurohumoral processes, can be one of the decisive factors that improve the course and outcome of the pathology. Thus, in recent ears, the modeling effect of antidepressants [11], substances affecting the cholinergic system, on efferent innervation [5,8] has been shown. However, the significance of the dopaminergic system in the implementation of the proinflammatory effect of flagellants remains insufficiently studied.

**THIS STUDY AIMS TO ELUCIDATE** the pathophysiological characteristics of the exudative and proliferative phases of the inflammatory response under the modulatory influence of dopamine receptor agonists.

## MATERIALS AND METHODS

The experiments were conducted on sexually mature male rats of outbred stock, with an initial body weight ranging from 165 to 185 g, maintained under standardized vivarium conditions. Each experimental cohort comprised 6–7 animals. The anti-exudative effect was evaluated using a model of acute inflammatory edema of the rat hind paw, induced by subplantar administration of 0.1 ml of dextran, histamine (0.1% solution), or carrageenan (1% solution) into the right hind limb [2,10].

Prior to the induction of inflammation, the test compounds were administered intragastrically 2 hours in advance. The first experimental group received sodium diclofenac (OAO Sintez, Russia) at a dose of 10 mg/kg, the second group was administered levodopa at 50 mg/kg, the third group received levodopa (Teva Pharmaceutical Enterprises Ltd., Israel) at 100 mg/kg, the fourth group was given bromocriptine at 5 mg/kg, and the fifth group received bromocriptine (Gedeon Richter, Hungary) at 10 mg/kg. The selection of these pharmacological doses was based on literature data [3,17,18]. The control (sixth) group received an equivalent volume of distilled water.

The volume of the right hind paw was measured at 60, 120, 180, and 240 minutes post-inflammatory agent administration using a plethysmometer (Ugo Basile Srl, Italy). The degree of anti-inflammatory activity (DAA) was

quantified based on the mean increase in paw volume, derived from parallel measurements, using the formula:

DAA = \left(\frac{V_k - V_o}{V_o}\right) \times 100\%

where V_k represents the mean increase in limb volume in the control group, and V_o denotes the mean increase in the experimental groups. A DAA value exceeding 30% was considered indicative of a pronounced anti-inflammatory effect [9].

To assess the influence of pharmacological agents on the proliferative phase of inflammation, a second series of experiments was conducted using the "cotton pellet granuloma" model in four groups of male albino rats. A sterile cotton pellet (10 mg) was implanted subcutaneously in the interscapular region under aseptic conditions and general ether anesthesia. From the day of implantation and for the subsequent seven days, animals in the first to third experimental groups were administered sodium diclofenac (10 mg/kg), levodopa (50 mg/kg), and bromocriptine (5 mg/kg) intragastrically once daily. Control animals received distilled water in an equivalent volume.

On the eighth day, the animals were sacrificed under ether anesthesia, and the granulomatous tissue surrounding the cotton pellets was excised, weighed using an electronic balance (SINKO, Japan), and subsequently dried at 60°C until a constant mass was achieved. The extent of the proliferative phase was determined by the difference between the final dry weight of the granuloma and the initial cotton pellet mass. The exudative response was evaluated by the difference between the wet and dry masses of the granulomatous tissue [4,9].

All experimental procedures were conducted in strict accordance with the "Guidelines for the Use of Experimental Animals" and the ethical standards outlined in the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes (ETS No. 123, Strasbourg, 18.03.1986).

The obtained experimental data were subjected to statistical analysis using the standard StatPlus 2009 software package, employing established methods of variance statistics. Statistical significance was determined by calculating mean values (M ± m) and comparing intergroup differences using Student's t-test. A probability value of $p < 0.05$ was considered statistically significant.

## RESULTS AND DISCUSSION

The experimental findings demonstrated that, within the first hour following dextran administration, the limb volume in the control group of rats exhibited a 132.9% increase relative to baseline measurements. This heightened edema response persisted for up to 2 hours, maintaining a plateau phase, after which a gradual decline in swelling was observed during subsequent measurement intervals (see Table 1).

Under identical experimental conditions, the prophylactic administration of sodium diclofenac, levodopa, and bromocriptine resulted in a statistically significant attenuation of inflammatory edema formation in the rat paw. These pharmacological agents exhibited notable anti-exudative activity, effectively mitigating the progression of inflammatory swelling.

**Table 1: Antiexudative Activity of Diclofenac Sodium, Levodopa, and Bromocriptine in the Dextran-Induced Edema Model**

| Groups | Dose mg/kg | Volume of the paw, $cm^3$ | | | | |
|---|---|---|---|---|---|---|
| | | Original | 1 hour | 2 hour | 3 hour | 4 hour |
| Control | - | 0,85±0,02 | 1,98±0,05* | 1,98±0,05* | 1,72±0,05* | 1,67±0,03* |
| Diclofenac | 10 | 0,85±0,03 | 1,52±0,08* | 1,37±0,07* | 1,22±0,07* | 1,12±0,06* |
| Levodopa | 50 | 0,82±0,03 | 1,65±0,03* | 1,54±0,05* | 1,31±0,04* | 1,29±0,09* |
| Levodopa | 100 | 0,85±0,02 | 1,76±0,06* | 1,66±0,06* | 1,66±0,01* | 1,12±0,02* |
| Bromocriptine | 5 | 0,84±0,01 | 1,60±0,05* | 1,54±0,04* | 1,45±0,05* | 1,27±0,05* |
| Bromocriptine | 10 | 0,87±0,02 | 1,68±0,04* | 1,63±0,04* | 1,39±0,04* | 1,24±0,03* |

Note: * - statistically significant differences compared to baseline data

As can be seen from Table 1, the effect of diclofenac sodium is clearly evident already one hour after the drug administration – its antiexudative activity was 40.7%, and in the following hours of the study it increased even more. It is evident that diclofenac sodium has a pronounced PVA in this model of aseptic inflammation. In contrast, in the group of animals receiving levodopa, the antiexudative effect of the drug was less pronounced at the beginning of the experiment, and more intense later. Thus, the decrease in the intensity of edema under the influence of the drug after 1 hour was 26.5% and 19.5%, and after 2 hours 36.3% and 28.3%, respectively, for doses of 50 and 100 mg/kg. In the following hours of the experiment, the observed effect increased and the PVA values at the end of the experiment were 43.7% and 67.1%, respectively. Additionally, similar changes were observed in animals that received bromocriptine prophylactically. Thus, one hour after the initiation of the inflammatory process, the drug significantly reduced the intensity of edema, with the increase in paw volume compared to baseline values being 190.5% and 193.1% for doses of 5 mg/kg and 10 mg/kg, respectively. The observed effect intensified in the subsequent hours. The calculation of the PVA after one hour from the start of the experiment showed values of 32.7% for the 5 mg/kg dose and 28.3% for the 10 mg/kg dose. In the following hours, this effect increased to 48.8% and 54.9%, respectively. It is well known that the process of dextran-induced edema formation during the first hour and subsequently is associated with mast cell degranulation and the release of inflammatory mediators such as histamine and serotonin. The inflammatory mediators released during this process increase the permeability of blood vessels, primarily venules and capillaries [6,7,10]. In light of this, a separate series of experiments was conducted to study the effect of dopamine receptor agonists on the course of histamine-induced inflammation.

The results of this series of experiments revealed that a subplantar injection of a 0.1% histamine solution leads to significant development of the exudation process, which is manifested by a marked increase in paw volume. As shown in Table 2, the degree of increase in paw volume 30 minutes after flagogen injection was greatest, reaching 254.4% relative to baseline values. Although the effect weakened slightly in subsequent periods, by the end of the first day of observation, it remained two times greater than baseline. This finding further highlights the critical role of histamine in the development of exudation, primarily due to its effect on increasing vascular permeability [6,10,20].

Histamine exerts a multifaceted effect on the human body. In particular, by stimulating H1 receptors located in blood vessels, bronchi, and the stomach, histamine increases vascular permeability, causes bronchial spasm, lowers blood pressure, and enhances gastric juice secretion [4, 9,]. Histamine is primarily detected at the site of inflammation simultaneously with the onset of tissue damage. It induces the dilation of blood vessels in the microcirculatory bed, increases their permeability, and stimulates the endings of pain nerves. Thus, histamine acts as a key trigger for acute inflammatory processes. The appearance of histamine at the site of inflammation is closely associated with mast cell degranulation. These cells then stimulate the synthesis of new mediators, the sources of which are lipids from the membranes of activated mast cells and basophils, including proteases, proteoglycans, eosinophil chemotactic factors, kinins, complements, eicosanoids, leukotrienes, platelet-activating factors (PAF), and others. In contrast, in animals that received sodium diclofenac as a preventive measure, the degree of exudation was significantly lower at all observation periods, and the PVA values in the initial period were 41%, after 1 hour - 38.3% and remained at a high level until the end of the experiment. We found changes of the same direction in rats that received levodopa, in which the PVA value in the studied observation periods ranged from 33.5% to 47%. A slightly

smaller effect was observed in animals that were pre-administered bromocriptine (26.7% - 40.9%).

Consequently, the analysis of the results in this series of experiments indicates that dopamine receptor stimulants prevent the development of the exudative phase of aseptic inflammation induced by histamine, and in their antiflagogenic activity are noticeably not inferior to sodium diclofenac. The presented results confirm the validity of the conclusion drawn up in the previous series of experiments. It can be assumed that dopamine receptor agonists have an antihistamine property. However, the relationship between dopamine receptors and histamine receptors has not been sufficiently studied. Therefore, it can be argued that the antiexudative activity of dopamine receptor agonists is associated with their peripheral adrenomimetic effect. The results of the experiments described above indicate that stimulation of the dopaminergic system prevents the development of the exudation process induced by acute-phase inflammation mediators. Considering the central role of the kinin system and prostaglandins in the pathogenesis of inflammation, the specific characteristics of the exudative phase in aseptic inflammation induced by carrageenan became a subject of considerable scientific interest. In the flagogenic action of the latter, as is known, an early period (in the first hours) is distinguished, when the main mediator is kinins, and in the late period (3-4 hours), prostaglandins are considered the main mediator [10,12,19].

The results of this series of experiments revealed that subplantar injection of a 1% carrageenan solution resulted in a progressive increase in paw volume relative to baseline, with increases of 63%, 87.7%, 113.7%, and 95.9%, respectively, at 1, 2, 3, and 4 hours following the initiation of the experiment. It is evident that the increase in paw volume was notably more pronounced at the 3 and 4-hour time points compared to the earlier stages of measurement. Preventive injection of sodium diclofenac shows a clear inhibitory effect on the exudation process. We have found a similar effect in rats that previously received levodopa and bromocriptine. Calculation of anti-inflammatory activity of the studied drugs showed that in the first hour the value of the PVA coefficient was 26.1%, 37.0% and 26.1%, and in the second 40.6%, 42.2% and 35.9%, respectively, of diclofenac sodium, levodopa and bromocriptine. It is noteworthy that in the subsequent terms the value of the PVA of the latter was somewhat high and was 50.6%, 47% and 42.2% after 3 hours, as well as 52.9%, 58.6% and 50% after 4 hours, respectively. The data clearly show that the studied drugs suppress the prostaglandin phase of corragenin to a greater extent. Thus, it can be assumed that in the antiflagogenic action of dopamine receptor agonists, an important place is occupied by the inhibition of the process of formation of prostaglandins, the leading mediator of inflammation. The anti-inflammatory effect of diclofenac sodium is due to the fact that it suppresses the activity of cyclooxygenase (COX), an enzyme that regulates the conversion of arachidonic acid into prostaglandins, an inflammatory mediator [4,13,21].

**Table 2:The Effect Of Levodopa, Bromocriptine And Diclofenac Sodium On The Course Of Aseptic Inflammation Induced By Histamine**

| Groups | Volume of the paw, $cm^3$ | | | | | |
|---|---|---|---|---|---|---|
| | original | 30 minutes | 60 minutes | 120 min. | 180 min. | 240 min. |
| Control | 0,69 ± 0,05 | 1,73±0,06* | 1,62±0,05* | 1,51±0,03* | 1,42±0,04* | 1,34±0,05* |
| Levodopa | 0,61 ±0,02 | 1,31±0,07* | 1,22±0,05* | 1,12±0,06* | 1,06±0,04* | 0,97±0,07* |
| Bromocriptine | 0,63 ±0,04 | 1,42 ±0,06* | 1,30±0,07* | 1,21±0,06* | 1,11±0,07* | 1,04±0,05* |
| Diclofenac sodium | 0,64 ±0,03 | 1,26 ±0,08* | 1,22±0,06* | 1,01±0,07* | 0,93±0,05* | 0,88±0,07* |

Note: * - statistically significant differences compared to baseline data

**Table 3:The Effect Of Diclofenac Sodium, Levodopa And Bromocriptine On The Course Of Aseptic Inflammation Induced By Carrageenan**

| Groups | Volume of the paw, $cm^3$ | | | | |
|---|---|---|---|---|---|
| | Original | 1 hour | 2 hour | 3 hour | 4 hour |
| Control | 0,73 ± 0,02 | 1,19 ±0,06* | 1,37 ± 0,05* | 1,56 ± 0,08* | 1,43 ± 0,05 * |
| Levodopa | 0,71 ± 0,03 | 1,05 ±0,04* | 1,09 ± 0,03* | 1,12± 0,04* | 1,0 ± 0,04* |
| Bromocriptine | 0,77 ± 0,02 | 1,06 ±0,06* | 1,14 ± 0,05* | 1,21 ± 0,04* | 1,06 ± 0,05 * |
| Diclofenac sodium | 0,80 ± 0,04 | 1,14 ±0,05* | 1,21 ± 0,05* | 1,28 ± 0,07* | 1,15± 0,04* |

Note: * - statistically significant differences compared to baseline data

In addition to inhibiting prostaglandins, other mechanisms of action of diclofenac sodium have been identified. Experimental investigations have demonstrated that this pharmacological agent significantly inhibits the migration of leukocytes to the site of inflammation. Additionally, diclofenac sodium appears to exert a modulating influence on the cytokine balance by reducing the concentration of pro-inflammatory interleukin-6 and elevating the levels of the anti-inflammatory cytokine interleukin-10 [15]. Such alterations in the cytokine profile favor a reduction in the secretion of pro-inflammatory mediators. Moreover, the reduction in free radical production, which occurs under the influence of diclofenac sodium, contributes to a decrease in the inflammatory response, thereby limiting its damaging effects on surrounding tissues [10,14]. Based on these findings, it can be hypothesized that under the influence of the dopamine precursor, there is a reduction in the release of inflammatory mediators from mast cells. It is also plausible that the activity of enzymes involved in the synthesis of prostaglandins and leukotrienes is suppressed. As levodopa is converted into dopamine within the mammalian body by the enzyme DOPA decarboxylase, which has an adrenomimetic effect, it can be inferred that the anti-inflammatory activity of the drug is primarily associated with the suppression of the exudative phase. Although the precise mechanism underlying this effect remains to be fully elucidated, it is reasonable to assume that it is related to the peripheral adrenomimetic effects of the dopamine precursor. This must be taken into account when optimizing therapeutic strategies for patients with dopaminergic system deficiencies.

Bromocriptine, a dopamine receptor agonist, exerts an anti-inflammatory effect, as evidenced by the reduction in paw edema observed in rats under conditions of aseptic inflammation. The PVA values obtained for bromocriptine do not significantly differ from those of the reference drug, sodium diclofenac. Interestingly, at lower doses, bromocriptine appears to exhibit a more pronounced anti-inflammatory effect compared to higher doses. This observed effect can likely be attributed to several factors. Firstly, bromocriptine may decrease the release of inflammatory mediators such as histamine and serotonin, which are known to increase vascular permeability, particularly in capillaries. As previously mentioned, the exudative phase of inflammation induced by dextran is associated with mast cell degranulation and the release of these mediators [6]. Secondly, bromocriptine is likely to exert a vasoconstrictive effect, helping to restore normal vascular permeability. Thirdly, it is plausible that bromocriptine affects the synthesis and release of interleukins and other cytokines. Finally, given the pivotal role of prostaglandins as key inflammatory mediators, it is reasonable to assume that bromocriptine may inhibit the synthesis of prostaglandins or their receptors. This could be related to the inhibition of cyclooxygenase, a mechanism

supported by literature indicating that dopamine receptor agonists negatively influence the gastric mucosal barrier. Consequently, caution is recommended when administering the drug to patients with erosive and ulcerative lesions in the gastrointestinal tract [1].

It is also important to note that bromocriptine, widely utilized in clinical practice for the treatment of conditions such as Parkinsonism, male hypogonadism, prolactinoma, benign breast diseases, and acromegaly, possesses distinct anti-inflammatory properties. These effects should be considered when designing pharmacotherapeutic regimens for the aforementioned pathologies.

In summary, the activation of dopamine receptors leads to a significant reduction in the intensity of edema formation in aseptic arthritis, underscoring the role of dopamine receptor activation in modulating the inflammatory response. The studied drugs used for the treatment of pathologies in the pathogenesis of which the reduction of the functional activity of the dopamine system plays a leading role - levodopa and bromocriptine, have a distinct anti-inflammatory effect. As is known, the inflammatory process occurs with the simultaneous development of three phases - exudation, alteration and proliferation. It has been established that the exudative stage of inflammation with increased permeability of various capillaries ends with the proliferation of mesenchymal cells [8,9,10,22]

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**Table 4.: Effect Of Diclofenac, Levodopa And Bromocriptine On The Proliferative Phase Of Inflammation In Rats**

| Groups | Dose mg/kg | Wet weight, mg | Dry weight, mg | Difference, mg |
|---|---|---|---|---|
| Control | - | 356,0±10,90 | 78,00±7,04 | 278,0±3,8 |
| Levodopa | 10 | 183,0±5,95* | 51,10±6,01* | 131,9±10,2* |
| Bromocriptine | 50 | 218,7±26,07* | 49,17±3,53* | 169,5±22,5* |
| Control | 5 | 229,3±20,16* | 53,50±5,82* | 175,8±14,3* |

Note: * - statistically significant differences compared to control data

Given that the pharmacological agents under investigation demonstrated a pronounced inhibitory effect on the exudative phase of inflammation, it became particularly relevant to assess their influence on the proliferative phase of the inflammatory process. The results from a separate series of experiments revealed that compounds that activate the dopaminergic system have a significant impact on the intensity of proliferative processes.

As illustrated in the data presented in Table No. 4, treatment with the reference non-steroidal anti-inflammatory drug sodium diclofenac led to a substantial reduction not only in the wet mass of the “cotton ball” but also in its dry mass, with reductions of 48.6% and 34.5%, respectively, in comparison to the control group of animals. A similar effect was observed in animals that were administered levodopa and bromocriptine. The data in Table No. 4 further indicate that the observed effects in these groups differed marginally from those seen in the sodium diclofenac-treated animals, although the general pattern of the results remained consistent.

**CONCLUSION:**

Thus, levodopa and bromocriptine, pharmacological agents commonly employed in the clinical management of pathologies associated with dopaminergic system dysfunction, exhibit a pronounced anti-inflammatory effect under conditions of aseptic inflammation induced by flagogens. These effects arise through distinct mechanisms of action observed in the experimental model, manifested by a significant reduction in the swelling of the rat paws. Both

levodopa and bromocriptine notably attenuate the intensity of not only the exudative but also the proliferative phases of the inflammatory response. In terms of anti-inflammatory potency, dopamine receptor agonists demonstrate activity comparable to that of the reference non-steroidal anti-inflammatory drug, sodium diclofenac, without significant differences in their efficacy.

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