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PHARMACOLOGICAL EVALUATION OF THE EFFECT OF INTERFERON INDUCERS ON THE EXUDATIVE AND PROLIFERATIVE PHASES ASEPTIC INFLAMMATION

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Abstract

This experimental study investigates the pharmacological effects of interferon inducers cycloferon, selagripp, and rutane on the exudative and proliferative phases of aseptic inflammation in a rat model. The results were compared with the effects of diclofenac sodium, a classic representative of non-steroidal anti-inflammatory drugs (NSAIDs). The findings revealed that the studied interferon inducers significantly inhibit the exudative process in the carrageenan-induced inflammation model, which is associated with a reduction in microcirculatory disturbances and a decrease in vascular permeability. At the same time, interferon inducers inhibit the proliferative phase of inflammation studied in the "Cotton-pellet" model. Concludes that pharmacotherapy with interferon inducers should take into account their antiexudative and anti-proliferative activity.

Keywords: Aseptic inflammation, interferon inducers, exudation, proliferation.

Annotatsiya

Ushbu eksperimental tadqiqotda interferon induktorlari — sikloferon, selagripp va rutanning kalamushlardagi aseptik yallig‘lanishning ekssudativ va proliferativ bosqichlariga farmakologik ta’siri o‘rganildi. Natijalar nosteroid yallig‘lanishga qarshi dori vositalar (NYAQDV) ning klassik vakili bo‘lgan diklofenak natriy ta’siri bilan solishtirildi. Tadqiqot natijalariga ko‘ra, o‘rganilgan interferon induktorlari karragenan bilan chaqirilgan yallig‘lanish modelida ekssudativ jarayonni sezilarli darajada to‘xtatadi, bu esa mikrosirkulyatsiya buzilishining kamayishi va qon tomir o‘tkazuvchanligining pasayishi bilan bog‘liq. Shu bilan birga, interferon induktorlari “paxta granulasi” modelida o‘rganilgan yallig‘lanishning proliferativ bosqichini ham susaytiradi.
Xulosa qilib aytganda, interferon induktorlari bilan farmakoterapiyada ularning antiekssudativ va antiproliferativ faolligini inobatga olish zarur.

Kalit so‘zlar: aseptik yallig‘lanish, interferon induktorlari, ekssudatsiya, proliferatsiya.

Аннотация

В данном экспериментальном исследовании изучено фармакологическое действие индукторов интерферона — циклоферона, селагриппа и рутана на экссудативную и пролиферативную фазы асептического воспаления у крыс. Результаты сравнивались с действием диклофенака натрия, классического представителя нестероидных противовоспалительных средств (НПВС). Полученные данные показали, что исследуемые индукторы интерферона значительно подавляют экссудативный процесс в модели воспаления, вызванного карагенином, что связано со снижением микроциркуляторных нарушений и уменьшением сосудистой проницаемости. В то же время индукторы интерферона ингибируют пролиферативную фазу воспаления, изученную на модели «ватного гранулёмы».

Таким образом, при фармакотерапии с использованием индукторов интерферона необходимо учитывать их антиэкссудативную и антипролиферативную активность.

Ключевые слова: асептическое воспаление, индукторы интерферона, экссудация, пролиферация.

Introduction. The main reason for the development of the overwhelming majority of violent diseases is inflammatory reactions, which are due to the activation of the immune system and constitute a protective reaction of the body. Inflammation is a universal response of the body to various harmful stimuli, and it is well known that this process leads to both local and systemic reactions. The latter can sometimes be excessively pronounced. The regulation of inflammation is a complex process. Endogenous substances produced by various cellular elements are involved in the development of inflammation. They release biologically active substances, including prostaglandins, leukotrienes, nitric oxide (NO), platelet-activating factor (PAF, PAFI), histamine, certain interleukins, and other mediators [1]. Therefore, the possibilities for pharmacological regulation of the inflammatory process are vast and diverse. These pharmacological effects are primarily aimed at inhibiting the synthesis and release of chemical substances and mediators that stimulate the inflammatory process. Such approaches target the molecular and cellular mechanisms of inflammation, helping to reduce adverse immune system responses. Currently, anti-inflammatory drugs are a mandatory component of pharmacotherapy for many diseases and pathological conditions. From this point of view, rational ways and means of suppressing the inflammatory process are of great practical importance.

Modern medicine has a significant number of different drugs that can affect the development of the inflammatory process. Nowadays, anti-inflammatory drugs are used in all areas of medicine, however, it should be noted that the use of anti-inflammatory drugs does not always provide the necessary therapeutic effect [2, 3].

Interferons, which belong to the cytokine group, are known to have antiviral, immunostimulant, and antiproliferative effects [4]. α, β, and γ interferons are high-molecular-weight proteins that activate various components of the immune system. Their immunotropic effect is manifested in the activation of macrophages, T-lymphocytes, and natural killer (NK) cells. Cycloferon, on the other hand, is a low-molecular-weight inducer of interferon synthesis and acts as an immunomodulatory agent with anti-inflammatory effects. This process primarily regulates the immune system, providing antimicrobial and immunosuppressive properties while modulating the inflammatory response[5, 6, 7].

Russian researchers have synthesized a number of interferon inducer drugs [7, 8]. However, their effect on the course of aseptic inflammation remains insufficiently studied. At the same time, their antiviral effect should not have a negative effect on typical pathological processes, such as inflammation.

Purpose. Comparative study of the effect of coelainfluenza, rutane and cycloferon on the exudative and proliferative phases of aseptic inflammation.

Materials and methods of research. The experiments were conducted using mature male rats with an initial weight of 170-180 grams. The experimental animals were kept in a vivarium with a natural light regime, at a temperature of 22-24°C and a relative humidity of 40-50%, and were provided with a standard diet. The animals were quarantined and acclimated in the vivarium for 14 days. Experimental groups of animals were formed with six animals each, taking into account their body weight. These experiments were carried out in full compliance with the Good Laboratory Practice (GLP) standards for preclinical re-

search and the Rules and International Recommendations of the European Convention for the Protection of Vertebrate Animals Used in Experimental Research (1986).

The model of carrageenan-induced paw swelling in laboratory animals was used as a simple screening test to evaluate the potential anti-inflammatory activity of compounds [9, 10]. The effect of the studied drugs on the exudative phase of inflammation was assessed using a model of aseptic inflammation induced by carrageenan. For this purpose, a freshly prepared 2% solution of carrageenan was injected subplantarily at a dose of 0.1 ml into the hind paw of rats. Study drugs were administered orally, with cycloferon at a dose of 10 mg/kg, celainfluenza and rutan at a dose of 25 mg/kg, and diclofenac sodium at a dose of 10 mg/kg, one day and one hour prior to carrageenan injection.

The severity of edema was determined by measuring the paw size of the rats compared to the control group using a special device called a plethysmometer (UGO BASILE, Italy). Before the start of the experiment, i.e., before administration of Phlogogen, the size of the rats' paws was recorded as the initial standard paw size and considered as 100% paw volume. The above property (PVA) of the compound with expected anti-iɳflammatory effect was developed according to the formula: PVA = (Vk – Vo) / Vk × 100%. Note: Vk is the average increase in the paws of the rats in the control group, and Vo is the average increase in the paws of the rats in the experimental group, determined under the conditions of the study.This methodological approach allows for a precise scientific evaluation of the anti-inflammatory efficacy of drugs during both the exudative and proliferative phases.

When studying the effect of the studied interferon inducers on the proliferative phase of inflammation, in rats under light ether anesthesia, hair was cut in the back area and a skin incision 1.0 – 1.5 cm long was made under aseptic conditions. After a one-week period, the rats were euthanized and removed from the experiment. The cotton balls, around which granulomas had developed, were carefully excised and subsequently dried to a constant weight at 75°C. The mass of the granulation-fibrous tissue was calculated by subtracting the mass of the implanted cotton ball from the mass of the dried granuloma [11]. In this experiment, the interferon inducers under investigation were administered once daily for a duration of 7 consecutive days, beginning from the day of cotton ball implantation.

Results and discussions. This experimental study compares with diclofenac sodium, which is used in many diseases as an anti-inflammatory, antipyretic, and analgesic [1,2]. The main «classic» sign of inflammation is the formation of swelling due to impaired microcirculation [3,10,11]. Based on the results of our experiments, it can be stated that under the influence of carrageenan, a significant increase in the size of the paws and feet was observed compared to the norm, which indicates that the compound has a sufficient anti-inflammatory effect. Thus, after the first 60 minutes of our experiment, the increase in the second was 84%, and after the next 60 minutes, this figure increased to 82%, 141.3%, and 131.7%, respectively. Based on the experiments conducted in the corresponding model, it can be concluded that the intensification of the exudation phase was more pronounced after 180 and 240 minutes compared to the previous one. This process is expressed in the fact that uɳder the influence of carrageenan, it proceeds in two phases: the first phase, triggered by the action of kinin, and the second phase, which occurs later (after 180 and 240 minutes) due to the action of prostaglandins. [12,13]. In animals screwed with interferon inducers, the development of exudation was less.

Under the conditions of the study, it was found that 60 minutes after oral administration of Phlogogen, the animals' paws increased in size by 66%, 76%, and 87%, respectively, as a result of the effects of coeloinfluenza, rutin, and cycloferon, compared to the coɳtrol group. The comparator drug diclofenac, as described above, also had a pronounced anti-inflammatory effect.

The increase in foot volume due to sodium administration was 47.8%. The anti-inflammatory efficacy of the drugs at this specific time point in the experiment was recorded as 23.1%, 13.5%, 3.7%, and 38.4%, respectively. As illustrated in Table 1, the observed therapeutic effect was enhanced with the progression of the follow-up period. The anti-inflammatory response of coeloinfluenza at 3 and 4 hours was 34.8% and 38.5%, respectively, rutane showed 47.2% and 45.8%, while cycloferon demonstrated 39.3% and 45.8%.

Table 1: Antiproliferative Activity Of Interferon Inducers

Groups	Wet granuloma weight (mg)	Effect %	Dry granuloma weight (mg)	Effect %
Control	356,4 ± 14,3	100	63,4 ± 4,9	100
Celagrip	178,3 ± 6,1*	50 (-50,0)	32,8 ± 3,1*	51,7 (-48,3)
Rutan	170,5 ± 5,4*	47,8 (-52,2)	31,0 ± 4,6*	48,9 (-51,1)
Cycloferon	199,6 ± 6,1*	56,0 (-44,0)	34,6 ± 5,3*	54,6 (-45,4)
Diclofenac sodium	168,6 ± 5,8*	47,3 (-52,7)	30,6 ± 4,1*	48,3 (-51,7)

Note: * - statistically significant differences compared to control

At the same time, in the group receiving diclofenac sodium, the anti-inflammatory activity was 43.8% and 49.4%, respectively. It can be seen that in this model of aseptic inflammation, interferon inducers show a distinct antiexudative effect and are not significantly inferior in their activity to diclofenac sodium. As noted, corrageenin-induced inflammation has two phases: the early stage is driven by the action of histamine, serotonin, and bradykinin, and the subsequent stage is associated with the action of prostaglandins, as well as increased cytokine production [12,13]. Based on the findings, it can be inferred that the kinin system likely plays a significant role in the mechanism of anti-inflammatory interferons, alongside its crucial involvement in the suppression of inflammatory mediators and the action of prostaglandins.

Cytokines, which are induced by interferon inducers, represent a group of polypeptide mediators that participate in the initiation and regulation of the body's immune defense mechanisms. The biological effects of these cytokines are mediated through highly specific receptor complexes, with cytokines binding to these receptors with exceptionally high affinity. It is important to note that individual cytokines may share common receptor subunits.

Based on their effect on the inflammatory process, cytokines can be classified into pro-inflammatory, which are involved in the initiation and perpetuation of inflammation, and anti-inflammatory, which modulate the resolution of inflammation. The pivotal pro-inflammatory cytokine is interleukin-1 (IL-1), while the principal anti-inflammatory cytokine is interleukin-10 (IL-10). Interferon inducers have a regulatory effect on innate immunity. The interferon-stimulated product of gene 15 (ISG-15) is a ubiquitin-like protein. The latter is induced by oxidative stress and protects cells from oxidative stress –

induced apoptosis. The level of reactive oxygen species leads to the development of a number of pathologies, including inflammation [4,15,16,17,18,19].

Along with the process of exudation in inflammation, the proliferative phase of this typical pathological process also develops at the same time. The development of the proliferative phase, accompanied by the formation of granulation tissue in the focus of inflammation, is not always positive during the pathological process. Almost all NSAIDs inhibit proliferative processes. The latter is studied on the implantation model of "cotton balls" - "Cotton-pellet" [3, 11].

Based on this, we studied the effect of interferon inducers on the proliferative phase of inflammation in a separate series of experiments. The results of experimental studies have shown that the studied pharmacological agents clearly suppress not only the exudative phase of inflammation, but also the proliferative phase of inflammation. As can be seen from the data in Table 2, under the influence of coeloinfluenza, rutane, cycloferon and diclofenac sodium, the weight of wet granulomas decreased by 50%, 47.8%, 56% and 47.3%, respectively. Therefore, these results confirm the conclusion drawn from the previous series of experiments that interferon inducers clearly suppress the exudative phase of inflammation.

Table 2: The Effect Of Interferon Inducers On Aseptic Inflammation Induced By Carrageenan

Groups	Original	Through ! hour	In 3 hours	In 4 hours
Control	0,65 ± 0,03	1,17 ± 0,05	1,54 ± 0,03	1,48 ± 0,04
Celagrip	0,61 ± 0,02	1,01 ± 0,05* 23,1%	1,19 ± 0,03* 34,8%	1,12 ± 0,03* 38,5%
Rutan	0,59 ± 0,04	1,04 ± 0,06 13,5%	1,06 ± 0,04* 47,2%	1,04 ± 0,04* 45,8%
Cycloferon	0,62 ± 0,05	1,16 ± 0,073,7%	1,16 ± 0,05* 39,3%	1,07 ± 0,05* 45,8%
Diclofenac sodium	0,67 ± 0,06	1,09 ± 0,05 38,4%	1,17 ± 0,06* 43,8%	1,09 ± 0,06* 49,4%

Note: * - statistically significant differences compared to control

- in the numerator the volume of affected paws (in ml)

- in the denominator the value of anti-inflammatory activity (in%)

Analysis of the resultis of graniloma dry matter showed that interferon inducers also

suppress the proliferative phase of inflammation. Thus, the mass of dry granulomas in animals treated with coeloinfluenza was low by 48.3%, rutan by 51.1%, cycloferon by 45.4%, while diclofenac sodium was reduced by 51.7%.

Thus, interferon inducers inhibit the processes of exudation and proliferation in aseptic inflammation. Simultaneously, in terms of pharmacological efficacy, the investigational drugs demonstrated comparable activity to the reference non-steroidal anti-inflammatory drug, diclofenac sodium. The mechanism of the anti-inflammatory effect of the newly isolated and studied substances under the studied conditions is generally accepted and directed. The anti-inflammatory effect manifests itself in the form of a decrease in the amount of kinin and an increase in the amount of anti-inflammatory interleukins. Compared with healthy and control animals, a 1.6-fold decrease in IL-1β was observed in the blood of animals chronically receiving the above compound compared to animals in the healthy and control groups. IL-1β is a peptide produced primarily by monocytes, macrophages, and endothelial cells of blood vessels. It exerts a pronounced effect on the vascular wall, eliminating leukocyte aggregation, stimulating the synthesis of endothelial factors that promote platelet aggregation, and normalizing procoagulant activity and the production of plasminogen activator.. These actions not only perpetuate the inflammatory cascade but also intensify its pathological effects. We have previously shown that aseptic inflammation is usually associated with an increase in the content of the anti-inflammatory cytokine IL-1β in the blood and a decrease in the content of the anti-inflammatory cytokine IL-10 [14,19,20,21,22].

Conclusion:

1. Interferon inducers have a distinct anti-exudative effect on models of corrageenin inflammation.

2. On the Cottonpellet model, interferon inducers reduce the mass of both wet and dry granulomas, indicating their antiproliferative activity.

3. In terms of their pharmacological activity, interferon inducers are not inferior to diclofenac sodium.

4. When administering pharmacotherapy with interferon inducers, it is crucial to consider their antiexudative and antiproliferative activities. These properties play a key role in modulating the inflammatory response, particularly in reducing fluid accumulation and inhibiting excessive cellular proliferation during the inflammatory process.

References

1. Xarkevich D.A. Farmakologiya. – Moscqua "GEOTAR-Media" 2021.
2. Khudarova A., Osadchuk M. NSAIDs – gastropathy: Prognazirovaniye techeŋiya i otodov [NSAIDs – gastropathy: Prognostirovaniye techeniya i otodov]. Doctor. 2018, No5, pp.17-23.
3. Khakimov Z.Z., Rakhmanov A.Kh., Mavlyanov Sh.R. Anti-inflammatory activity of a mixture of extracts of medicinal plaŋts. Monograph //LLC "TIBBIYOT" NFSHRIYOT MATBAA UYI Tashkent -2012, -215 p.
4. Nfrovlyansky A.N., Poposkov V.V., Ivanova A.M. et av. Interferon – regulating activitu of the celagrip antiviral drug and its influence of formation of reactive oxygen species and expressioŋ of innate immunity genes in the follicular imphoma patients. // PROBLEMS OF VIROLOGY. 2020; 65.(5). P. 284-293.
5. Khakimov Z.Z., Rakhmanov A.Kh., Rakhimbaev A.A. Opredelenie anti-iŋflammatory activity of cycloferon. Infection, Immunity and Pharmacology. 2014 T.2. No. 3, pp. 199-202.
6. Bazhanova U.D. Cycloferon: Mechanism of Action, Fuŋction and Application in the Clinic. - 2012 – vol. 75, No. 7. P.40-44.

7. Sarimsakov A.A., Rashidova S.Sh., Aripova T.U. Novoye profilaktike i lechenie viral'nogo grippa i ARVI [New preveηtion and treatment of viral influenza and ARVI]. Monograph. Tashkent. 2010. 112p.
8. Salikhov Sh.I., Kim R.Yu., Mavlyanov S.M., et al. Opredelenie antigriposnoy aktivnosti preparatov na osnove polypheηolov vegetnogo raw material [Determination of antigriposis activity of preparations based on polyphenols of plant raw materials]. Medical Journal of Uzbekistan. -2007. -№5. –pp.64-67.
9. Kong Kh.Kh., Sibgitullina R.R., Khabibrakhmanova A.M. et al. It is possible to use cell-based test systems to screen for the anti-iηflammatory activity of new 5(S) methyloxy derivatives of 2(5H)-furanone. Kazan Medical Journal. -2017. –Volume 98. №2. P.211-217.
10. Kong Kh.Kh., Khaziakhmetova I.N., Ziganshina L.E. Modeling Iηflammatory Edema: Are the Models Interchangeable? Experimental and Clinical Pharmacology. -2015. –Volume 78, No.7.-P.24-31.
11. Mironov A.N. Rukovodstvo po provedeniya doklinicheskikh issledovaniy drugeskikh sredstva [Guidelines for coηducting preclinical research of medicinal products]. Part One. Moscow, Grif i K Publ., 2012. 944 p. (in Russian).
12. Necas J., Bartosikova I., Carrageeηan: a review// Mediciηe. -2013.-Vol.58, No4. –p.187-205.
13. Khakimov Z.Z., Rakhmaηov A.Kh., Mavlanov Sh.R. Study of the Influeηce of Dry Extrakt of Medicinal Plants on the Course of Carragteηan –Induced Inflammation/ //American Jurnal of Medicine and Medical Sciences. -2019. -Vol.9, -P.307-310.
14. Khakimov Z.Z., Abduvaliev A.A., Rakhmanov A.Kh., Mavlanov Sh.R. Vospleniya sukhogo extracta mediciηal'nykh rastenii na soderzhenie kortisol, interleukinov IL-1β i IL-10 pri asepticheskogo vostomenii [Spleniya dry extract of medicinal plants on the content of cortisol, interleukins IL-1β and IL-10 in aseptic inflammation]. Sports medicine. 2019. No3-4, pp.56-59.
15. Kamilov X. et al. Development of composition and techηology of antidiabetic tablets based on medicinal plants //BIO Web of Conferences. – EDP Sciences, 2024. – T. 149. – C. 01047.
16. Khakimov, Z. Z., and G. Yu Djanaev. "Askarov OO Study Of the Effect of a Mixture of Extracts of Medicinal Plants on the State of the Gastric Mucosa in Gastropathυ Induced by Indomethacin." *Eurasian Medical Research Periodical* 19 (2023): 90-95.
17. Аллаева М. Ж., Джанаев Г. Ю., Ачилов Д. Д. Achillea millefolium l. ўсимлиги қуруқ экстрактининг қон ивиш жараёнига таъсириηи ўрганиш изучение влияния сухого экстракта achillea millefolium l. на свертывающее системы крови Тошкент тиббиёт академияси //ўзбекистон фармацевтик хабарномаси. – Т. 61.
18. Djanayev, G. Y. "Dorivor o ‘simliklar quruq ekstraktining rezerpinli me'da yarasiga ta'siri: дис." *Tibbiyotdagi zamoηaviy ilmiy tadqiqotlar* (2022).
19. Djanaev, G. Y., Kh, K., Askarov, O. O., & Sultanov, S. A. (2023). Pharmacotherapυ of Gastropathy (Literature Review). *Texas Journal of Medical Science*, *17*, 67-76.
20. Allaeva, M. Z., et al. "Influence of lesbochol dry extract on the current of experimeηtal nervo-reflective gastric ultra." *European Journal of Molecular and Clinical Medicine* 7.3 (2020): 2749-2753.
21. Худайбердиев Х. и др. Эффективность глицерама в восстановлении функционального состояния печени при ее остром токсическом поражении глицерам при остром токсическом пораженηи печени //Журнал биомедицины и практики. – 2021. – Т. 1. – №. 3/2. – С. 250-255.
22. Kholmatov, J. A., Kawale, K. V., Jalilov, F. S., Kakhkharova, S. B., & Djanaev, G. Y. (2025). USE AND IMPORTAHCE OF MEDICINAL PLANTS IN BURNS. *JOURNAL OF MEDICINE AND PHARMACY*, *8*(1), 1-10.