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**CHRONOPATOLOGICAL FEATURES OF CARRAGEENAN’S ACTION**

RESUME

The results of the study of сhronopatological features carrageenan’s action in different seasons. It is shown that depending on the season the reaction to flogogen’s injection varies and is characterized as the rate of development, and on the severity. The reasons for these differences are biological rhythms of melatonin and cortisol, which vary depending on the season.

**Key words:** chronopharmacology, inflammation, karrageenan.

**Introduction.** Creating new drugs are inextricably linked with conducting various studies of promising biologically active substances (BAS) on model pathologies. For BAS offered as antiinflammatory agents, one of the classic models to study the antiinflammatory (antiexudative) properties are karrageenan-induced paw edema in rats [2,4].

In the last 30-40 years has increased scientific interest in the study of chronopatology and chronopharmacology [1, 3, 5]. Therefore, the study chronopharmacolgical features of the existing antiinflammatory drugs and promising BAS impossible without knowledge of the chronofeatures of actions of the agents used when playing pathology model of inflammation.

The purpose of this study was to investigate the characteristics of action carrageenan in different seasons.

**Materials and methods.**

The object of the study was the classic model of inflammation – carrageenan-induced paw edema in rats. Inflammation was caused by injection of 0.1 ml of 1% solution of carrageenan in every season of the year at 22 hours, as rats are night animals. Measuring the size of edema in conditional units (cu) held by a mechanical onkometr, hourly for 12 hours after administration of carrageenan [2].

Acrophase - the biggest size in the rat paw edema [5]. The amplitude (magnitude) edema during akrofaza was calculated by the difference rat paw size before and after the introduction of carrageenan. Mezor (average of the studied parameters for 1 cycle) described the rate of disappearance of edema.

Experiments were carried out in October, January, April and July, because these months seasonal biorhythms of the body are the most stable and the best reflect the state of the organism during a certain season [4, 7, 8]. Experiments were repeated three times during the period of the year, in order to identify possible contingencies and confirm the reproducibility of results Results were raised by 3 series of experiments in each of the periods. Each series consisted of intact control group and the control group pathology.

**Results and discussion.**

The results are presented in Fig. 1-2 and in Table. №1.

During autumn at 22 hours acrophase of inflammatory edema was 55,6 ± 1,25 cu observed for 5 hours after administration of carrageenan, while in winter it was observed at 4 hours, and the spring and summer - 3 hours (Fig. 1). Edema developed autumn slowest compared to other seasons (from 1 to 5 hours). The amplitude at fifth hour of the experiment (acrophase) after carrageenan injection was − 23,5 ± 1,05 cu. Mezor was 43,85 ± 3,92 cu. Reducing edema passed slowly, edema did not disappear (47 ± 1,2 cu) within 24 hours after the carrageenan administration (Table. №1).

During winter acrophase of inflammatory edema was observed at 4 hours after administration of carrageenan (Table. №1), and 1 hour earlier then in autumn, but its value is not significantly different from that seen in autumn (51,5 ± 0,33 cu) (Fig. 1). Edema developed for 1 hour slower than in spring and summer (acrophase observed at 3 hours). The amplitude of edema in acrophase in winter was 19,17 ± 0,61 cu. This indicates that the intensity of edema was lower compared to autumn (23,5 ± 1,05 cu) and summer (32,14 ± 0,94 cu). Mezor (41,92 ± 3,18 cu) Was similar to autumn (43,85 ± 3,92 cu). Reducing the edema took place faster compared with the autumn group: at sixth hour of the experiment (2 hours after acrophase) edema decreased by 7 cu, and for 12th hour − by 12.67 cu, while in autumn in the same time of experiment, these values were respectively 4.1 cu and 8.6 cu about. (Table. №1).

Thus, the activity of proinflammatory effect of carrageenan during autumn and winter is about the same, indicating that similar mechanisms of inflammatory response to its input.

Spring acrophase of inflammatory edema was observed as in summer, at third hour, that is 1 hour earlier than in winter and 2 hours earlier than the autumn and was 53,75 ± 1,54 cu. (Fig. 1). Mezor was 44,13 ± 3,3 cu. Speed of edema developing was the largest (acrophase observed at 3 hours after administration karaheninu, while winter - 4, and in the fall - at 5). The amplitude of 3 hours after administration of carrageenan was 19,25 ± 1,48 cu, but decreased edema slowest compared with edema in other seasons: 2 hours after acrophase edema decreased only by 2.67 cu compared to acrophase, while the autumn - 4.1 cu, in winter - 7 cu, and summer - at 6.43 cu. (Table. №1). After 12 hours of observation in the spring edema decreased by 9.92 cu compared to acrophase that was not significantly different from the values fall 8.6 cu, but was significantly less than 12.67 cu in winter and 17 cu in summer.

In summer you type karaheninu 22 hours acrophase inflammatory edema was observed also for 3 hours after administration of carrageenan (Fig. 1). The rate of edema was similar to the spring season: acrophase observed at 3 hours, while in winter - 4, and in the fall - at 5, and its value was 64 ± 0,8 cu. (Fig. 1), the highest value compared to other seasons. The amplitude of 3 hours after administration flohohenu was 32,14 ± 0,94 cu far the largest volume compared to 19,25 ± 1,48 cu in spring, 23,5 ± 1,05 cu in autumn and 19,17 ± 0,61 cu in winter. The rate of reduction of edema was not significantly different from the winter season, but was significantly lower compared to spring and autumn: 2 hours after acrophase edema has decreased by 6.43 cu, while the fall - 4.1 cu, in spring - at 2.67 cu, and in winter - 7 cu. After 12 hours of observation edema summer decreased by 17 cu, which is also the largest value compared with 8.6 cu in autumn, 12.67 cu in winter and 9,92 cu in spring (Table 1).

Reasons for changes in activity karaheninu in different seasons (Fig. 2) can be explained by the peculiarities of biological rhythms of melatonin and cortisol. In autumn and winter, when sunlight little more melatonin is synthesized and endogenous glucocorticoids less [5, 6], as manifested stronger inflammatory swelling and decreases slowly. Spring and summer are, by contrast, melatonin is synthesized less cortisol and more - and it inhibits the development of edema and promotes its rapid reduction [5, 6]. In addition to the speed of onset akrofazy swelling affects the overall reactivity, as it is known to decrease the fall and winter, and spring and summer growing [5].

*Fig. 1. Carrageenan activity in seasons of the year.*

\* − rat paw volume before administration of carragenan

*Fig. 2. Comparison of the activity of carrageenan on the season.*

*Table 1*

**Сезонний хронопортрет карагеніну**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Показник | Autumn | Winter | Spring | Summer |
| Acrophase | size, cu | 55,6±1,25 | 51,5±0,33 | 53,75±1,54 | 64±0,8\* |
| the timing, h | 5 | 4 | 3 | 3 |
| Mezor | 43,85±3,92 | 41,92±3,18 | 44,13±3,3 | 47,93±5,32 |
| Amplitude | 23,5±1,05 | 19,17±0,61 | 19,25±1,48 | 32,14±0,94\* |

\* − significant difference relative to the winter and spring (р > 0,05)

**Conclusions.**

Thus, as the analysis of the results of research chronopatological features of carrageenan action showed, the rate of development and expression of aseptically-exudative inflammatory reaction to this agent is different in different seasons, so it is necessary to consider the conduct of preclinical studies and comparison of anti-inflammatory (antiexudative) properties of promising BAS at this model. Thus, the rate of edema and acrophase are the biggest during summer and spring, while the largest amplitude observed in summer and the lowest - in the winter. Reducing edema occurred the most rapidly in summer and the slowest - in the autumn.

So rationally continue studying chronofeatures of agents action on other models used in preclinical studies antiinflammatory drugs.

Due to the fact that rats are nocturnal animals received results of preclinical studies need to be correctly extrapolated for further guidelines.

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