# TIME COURSE OF CARRAGEENIN INFLAMMATION UNDER TREATMENT WITH LITHIUM HYDROXYBUTYRATE

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Lithium hydroxybutyrate has a broad spectrum of action and exhibits its activity in widely different pathological states [2]. The writers showed previously [1] that this compound, if given prophylactically, inhibits the development of peritonitis in rats caused by intraperitoneal injection of silver nitrate, and edema of the limbs caused by subplantar injection of biologically active substances which are mediators of inflammation. One of the most important criteria for evaluation of the compound as an anti-inflammatory agent is its ability to inhibit the development of carrageenin inflammation [8].

In the present investigation the time course of carrageenin inflammation was studied during therapeutic application of lithium hydroxybutyrate.

## EXPERIMENTAL METHOD

Experiments were carried out on 40 male Syrian hamsters weighing 180-200 g and on 30 male Wistar rats weighing 120 g. The pathological process developing in the mucous membrane of the retrobuccal pouch of the hamsters in response to application of 0.5 ml of a suspension of 500 μg carrageenin was chosen as one model of inflammation; 0.5 ml of isotonic sodium chloride solution was applied to the control animals. The time course of the microhemovascular responses in the mucous membrane was studied biomicroscopically by the transparent chamber method [4]. The external diameter of the arterioles (40-45 μ) and venules (50-55 μ) was measured with an ocular micrometer. The period of observation lasted 5 days. The amount of edema, the temperature, and pain sensitivity of the hind limbs of rats after subplantar injection of 0.1 ml of a suspension of 500 μg carrageenin in isotonic sodium chloride solution was estimated in the second model of inflammation; 0.1 ml of isotonic sodium chloride solution was given to the control animals by subplantar injection. Before and 1, 2, and 3 h after injection the volume of the limb was measured in a measuring cylinder, the skin temperature was determined (TPEM-1 thermometer) and the nociceptive response was assessed by means of an Analgesimeter for the Rat Paw (Italy). Lithium hydroxybutyrate was injected subcutaneously

TABLE 1. External Diameter of Microvessels of Mucous Membrane of Hamster Retrobuccal Pouch on 4th Day of Carrageenin Inflammation, with Therapeutic Administration of Lithium Hydroxybutyrate (M ± m)

| Experimental conditions | Number of measurements | Diameter, μ | |
|---|---|---|---|
| | | of arterioles | of venules |
| Control | 20 | 42,9±0,4 | 51,7±0,4 |
| Lithium hydroxybutyrate | 20 | 43,5±1,2 | 55,2±0,8 |
| Carrageenin | 12 | 56,5±2,0* | 66,6±1,3* |
| Carrageenin + lithium hydroxybutyrate | 18 | 41,6±1,5 | 54,0±0,9 |

Legend. *p < 0.001 compared with control.

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TABLE 2. Changes in Volume, Temperature, and Threshold of Pain Sensitivity of Rat Hind Limbs following Subplantar Injection of Carrageenin and Therapeutic Administration of Lithium Hydroxybutyrate (M ± m; n = 10)

| Time of investigation | Experimental conditions | Volume of limb, ml | Skin temperature, °C | Pain threshold, g |
|---|---|---|---|---|
| Before injection | Control | 0,91±0,12 | 24,3±0,4 | 312±24 |
| | Carrageenin | 1,32±0,15 | 23,8±0,7 | 287±16 |
| | Carrageenin + lithium hydroxybutyrate | 1,13±0,14 | 21,5±0,2 | 294±29 |
| After injection | | | | |
| 1 h | Control | 0,85±0,11 | 23,6±0,6 | 288±31 |
| | Carrageenin | 2,82±0,11* | 30,1±0,6* | 127±16* |
| | Carrageenin + lithium hydroxybutyrate | 1,34±0,19 | 22,4±0,8 | 301±35 |
| 2 h | Control | 0,94±0,15 | 24,8±0,3 | 320±42 |
| | Carrageenin | 1,51±0,13 | 23,9±0,4 | 291±32 |
| | Carrageenin + lithium hydroxybutyrate | 1,23±0,15 | 21,9±0,3 | 294±32 |
| 3 h | Control | 1,02±0,19 | 23,5±0,2 | 321±39 |
| | Carrageenin | 2,57±0,10* | 29,9±0,7* | 140±23* |
| | Carrageenin + lithium hydroxybutyrate | 1,05±0,12 | 22,3±0,2 | 320±42 |

Legend. *p < 0.05 compared with control.

in the dorsal region in a dose of 200 mg/kg 30 min after injection of carrageenin. The results were subjected to statistical analysis [3].

## EXPERIMENTAL RESULTS

The study of the action of carrageenin on the mucous membrane of the retrobuccal pouch of the hamsters showed that 1 day after application of this phlogogen two of 10 of the animals developed necrosis of the mucous membrane. Another two hamsters developed necrosis on the 2nd and 3rd days. In the remaining animals, during periodic observation of the microhemocirculation in the mucous membrane, on the 1st day of inflammation slowing of the blood flow and aggregation of erythrocytes in the venules were observed. After 2 days aggregation of erythrocytes in the venules were observed. After 2 days aggregation of erythrocytes began in the capillaries, in the form of "rouleaux," and plasmatized vessels appeared. On the 3rd day, slowing of the blood flow took place in the arterioles, with pavementing of the leukocytes in the venules, and escape of leukocytes and erythrocytes from the venules into the surrounding tissue by diapedesis. On the 4th day stasis appeared in many capillaries and venules. At the same time the external diameter of the measured arterioles and venules reached its maximal value compared with the control (Table 1). On the 5th day the blood flow ceased in all microvessels of the mucous membrane.

Meanwhile, after administration of lithium hydroxybutyrate, necrosis of the mucous membrane of the retrobuccal pouch was observed in only one of 10 animals, on the 4th day after application of carrageenin. In the remaining nine hamsters, there were no marked disturbances of the microhemocirculation throughout the period of observation. The diameter of the microvessels was unchanged (Table 1).

In the other series of experiments, carried out on rats, subplantar injection of carrageenin caused a biphasic response of inflammation in the limb tissues. Edema of the limbs (increased vascular permeability), elevation of the skin temperature and erythema, a more intensive pain response, and limitation of movement in the tarsal joint took place 1 h after the injection. During the next hour these inflammatory changes subsided. The changes then recurred, and reached the maximum 3 h after injection of the phlogogen (Table 2).

Lithium hydroxybutyrate inhibited the development of both the first and the second phases of the inflammatory reaction induced by carrageenin (Table 2).

This investigation, using different models and two species of animals, thus demonstrated for the first time that lithium hydroxybutyrate, when given therapeutically, can inhibit the development of carrageenin-induced inflammation, restore the normal microhemocirculation and vascular permeability, and thus help to maintain tissue hemostasis.

According to some data [9, 11] the first phase of edema of the limb in rats induced by carrageenin depends on the release of biogenic amines (histamine and serotonin) from their depots, whereas the second is connected with disturbance of synthesis of prostaglandins, which are modulators of the inflammatory process, in the focus of inflammation [5, 7, 12]. It can be tentatively suggested that lithium hydroxybutyrate can inhibit release of hista-

mine and serotonin from the depots at the beginning of the inflammatory reaction. We know [6] that lithium reduces the release of catecholamines from adrenergic endings. Since in the second model of inflammation the pain syndrome (pain stress) was dominant [11], during which the secretion of catecholamines from the adrenals and adrenergic endings is increased [10], lithium hydroxybutyrate may perhaps depress this process and thus inhibit prostaglandin synthesis in the second phase of inflammation. Consequently, lithium hydroxybutyrate, together with other preparations, may prove to be effective in the treatment of both early and late stages of inflammatory processes, in which prostaglandin synthesis is disturbed.

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# CHANGES IN THE AIR-BLOOD BARRIER OF THE LUNGS DURING HYPERTHERMIA


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It is generally considered that the response of lung tissue to exogenous and endogenous influence is realized in the form of a stereotyped response of cells composing the air-blood barrier (ABB) of the lungs. This response is based on a change in permeability of the ABB of the lungs and, in particular, of the biological membranes composing its structures, and this ultimately leads to an increase in the degree of hydration of lung tissue and to edema of the lungs [1, 4, 8, 13]. This type of picture is observed during the development of anoxic stages of varied genesis in the body [7, 10, 12]. The disturbances observed may have a significant influence on the effectiveness of oxygenation of the blood in the lungs; the effect of a rise of body temperature on ultrastructure and function of the ABB has received less study. In that state disturbances of the ABB may arise, on the one hand, as a result of the development of an anoxic state of predominantly circulatory genesis, whereas on the other hand the direct action of a high temperature on the lung tissues cannot be ruled out. Whereas edema and dystrophic changes have been shown to take place in the structures of the cardiovascular system during hyperthermia [5, 6], the respiratory apparatus has been inadequately studied from this standpoint.

The aim of this investigation was to study the effect of hyperthermia on the ultrastructure and morphometric characteristics of ABB of the lungs.

## EXPERIMENTAL METHOD

Experiments were carried out on six mongrel dogs weighing 14-18 kg and anesthetized with chloralose (80 mg/kg) and urethane (300 mg/kg). Hyperthermia was induced in a hot and humid


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