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RESEARCH OF COXIBS EFFECT ON MNESTIC ACTIVITY OF LABORATORY RATS

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Abstract. Coxibs are innovative medicines of the group of non-steroidal anti-inflammatory drugs based on benzenesulfonic acid: celecoxib, rofecoxib, eterocoxib, parecoxib, valdecoxib, lumiracoxib. Presently, celecoxib and rofecoxib are most commonly used. Object and methods. Experimental study of non-steroidal anti-inflammatory drugs of the coxib group (rofecoxib and celecoxib). In an experiment on laboratory rats, the effect of rofecoxib and celecoxib on mnestic activity of laboratory rats was investigated on the model of the conditioned reflex of passive avoidance under formalin edema. Results. Analysis of the experimental study results indicates that celecoxib has a positive effect on formation of mnestic activity in rats. Conclusions. Administration of celecoxib in laboratory rats under conditions of formalin edema contributes to generation of short-term memory.

Key words: coxibs, celecoxib, rofecoxib, conditioned reflex of passive avoidance, formalin edema.

Introduction. Currently, there is a wide variety of modern non-steroidal anti-inflammatory drugs (NSAIDs) that are used to treat many diseases, from fever to severe autoimmune processes. NSAIDs includes medicines of various chemical composition, but most NSAIDs are organic acids as to their chemical structure, therefore able to be accumulated in the focus of inflammation. This contributes to a clear anti-inflammatory effect. Owing to the significant anti-inflammatory, analgesic and antipyretic action, NSAIDs are commonly used in many fields of modern medicine. But development of undesirable effects (peripheral edema, gastro-, hepato-, oto-, nephrotoxicity, hypersensitivity, skin manifestations, neurological symptoms) complicates their use [1, 2]. Despite the fact that the Ukrainian pharmaceutical market is full of NSAIDs, search for new and non-toxic medicines from this group is the subject of preclinical and clinical research by modern scientists [2].

Coxibs are innovative medicines of NSAIDs based on benzenesulfonic acid: celecoxib, rofecoxib, eterocoxib, parecoxib, valdecoxib, lumiracoxib. Presently, celecoxib and rofecoxib are most commonly used [3].

Celecoxib is one of the most popular NSAID in the world, being among 100 most popular medicines [4], effectively relieving of acute pain in traumas, surgeries, acute pathology of the musculoskeletal system [5]. The medicine also proved itself to be good as an urgent analgesic [6, 7], is an effective agent for chronic pains control in rheumatoid diseases [8]. Celecoxib is the only NSAID for which it has been reliably proven that the frequency of complications in all departments of the gastrointestinal tract gets reduced. It rather rarely causes cardiovascular complications [9]. According to [10] celecoxib is a promising agent in treatment of schizophrenia, since it is believed that inflammation plays a significant role in development of neurodegenerative processes in this pathology.

Celecoxib as to its chemical constitution is (4-[5-(4-Methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide) (Fig. 1).

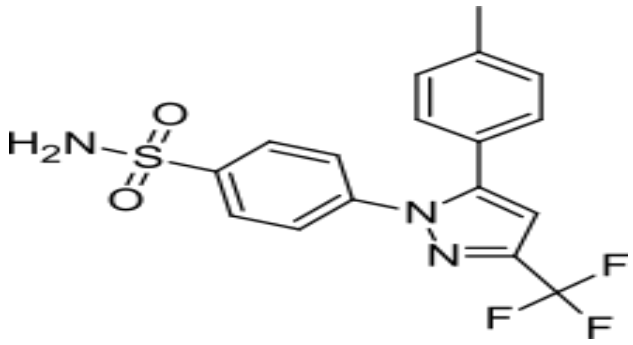

Fig. 1. Celecoxib (4-[5-(4-Methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide), $C_{17}H_{14}F_3N_3O_2S$

Anti-inflammatory, antipyretic and analgesic effects of coxibs, like any NSAID, are associated with anti-prostaglandin activity. Thus, *in vitro* the ability of celecoxib to block cyclooxygenase-2 (COX-2), depending on the method, is (10-3000) times greater than that of cyclooxygenase-1 (COX-1) [3].

Rofecoxib is the second medicine of the coxib group after celecoxib, released for wide clinical use [11]. Rofecoxib (4-[4-(methylsulfonyl)phenyl]-3-phenyl-2(5H)-furanone) is NSAID, a synthetic preparation of the coxib group having a side sulfone chain in its structure (Fig. 2):

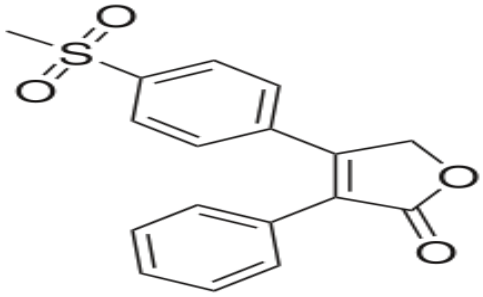

Fig. 2. (4-[4-(methylsulfonyl)phenyl]-3-phenyl-2(5H)-furanone, $C_{17}H_{14}O_4S$

Rofecoxib is a highly selective inhibitor of COX-2 isoform, which is generated only in the focus of inflammation and enables transformation of arachidonic acid into prostaglandins (PGs). Coxib molecules have a rigid side chain that allows these medicines to penetrate into the cavity inside COX-2 molecule and interact with this specific COX isoform [12]. Rofecoxib has an expressed analgesic and anti-inflammatory effect, comparable in strength to other NSAIDs, has a chondroprotective effect, reduces concentration of prostaglandins in cerebrospinal fluid, which leads to inhibition of secondary hyperalgesia development allowing use of this medicine in traumas and for postoperative pain syndrome relief [13].

Coxibs in their effectiveness are not inferior to classic NSAIDs, but they are far superior in terms of use safety, therefore they were chosen for research [14].

The purpose of our study is to research the effect of NSAID from the coxib group (rofecoxib and celecoxib) on mnestic activity of laboratory rats on the model of the conditioned reflex of passive avoidance (CRPA) under conditions of formalin edema (f. e.).

Object of study. Experimental study of NSAID of the coxib group (rofecoxib and celecoxib).

Research methods. Experimental studies of biological activity were conducted at the Medical and Bioorganic Chemistry Department of Kharkiv National Medical University (KhNMU) on laboratory animals: 30 sexually mature WAG rats of the Wistar population weighing 180-280 g of both sexes. The research was performed in accordance with the methodological recommendations of the State Pharmacological Center of the Ministry of Health of Ukraine [15]. The conversion from human doses to rats was performed using the species sensitivity coefficient of Rybolovlev Yu. R. [16]. The economical approach, bioethical rules and statistics requirements were considered when selecting the number of animals and dividing them into groups.

The work was carried out on laboratory animals from the experimental-biological clinic of KhNMU, taking into account the standards of storage, care and feeding (air temperature – 23-25˚C, lighting – 100 lx in the room, 20-40 lx in the cage [17]. Duration of laboratory animals stay – 1.5 months; acclimatization period – 2 weeks; basic diet – vegetables, fodder beet; water source – settled tap water. The rats were kept under vivarium according to the rules of humane treatment for laboratory animals. The studies have been carried out in compliance with the principles of the "European Convention for the Protection of Vertebrate Animals used for Experimental and Scientific Purposes" (Strasbourg, 1986) [18], Directive 2010/63/EU of the European Parliament and the EU Council "On Protection of Animals Used for Scientific Purposes" (Brussels, 2010) [19] Directive 2010/63/EU of the European Parliament and of the Council on the European Union «On the Protection of Animals Used for Scientific Purposes» (Brussels, 2010) [26] and

«General Ethical Principles for Experiments on Animals» (Kyiv, 2001), the Decree of the First National Bioethics Congress (Kiev, 2009) [20]. Experiments were conducted in the first half of the day, which according to the literature agrees with the dependence of the basic pharmacological parameters and pharmacological activity of the medicines taken from the circadian rhythms [21, 22].

Statistical processing of the data was carried out using generally accepted methods of statistical analysis (mean, mean average error, Fisher Student's exact probability test) using MS Excel and Stat Graphics Plus 2.1 programs [23].

The animals were divided into 5 groups of 6 animals each. The animals of the 1st control group were once intragastrically administered 3% starch mucus (2 ml per 200 g of rat`s weight). Animals of the 2nd to 5th groups were simulated to have f. e. by sub-plantar administration 0.1 ml of 2% formalin solution into the hind paw of rat [15]. Animals of group 2 were intragastrically administered 3% starch mucus (2 ml per 200 g of a rodent weight), those of groups 3-5 were once intragastrically administered 3% starch mucus as suspension mixed with experimental medicines: animals of the 3rd group – rofecoxib (1.3 mg/kg), of the 4th group – celecoxib (5.0 mg/kg), of the 5th group – reference drug sodium diclofenac (8 mg/kg). The maximal development of f. e. was observed 4 hours after its simulation [15]. Medicines and 3% starch mucus (control group) were administered 1 hour before that, considering their pharmacokinetic characteristics.

The effect of rofecoxib, celecoxib on mnestic activity of the central nervous system of laboratory rats was studied on the model of CRPA under conditions of f. e. [24].

Research results. In this study, we set out to research the effect of coxibs (celecoxib and rofecoxib) on mnestic activity of laboratory rats on the model of CRPA under the conditions of f. e. that has not been experimentally investigated before.

The effect of f. e. on mnestic activity of the brain of rats showed a pronounced tendency to decrease the latent period of the reflex (67.8 ± 17.7 s against 72.2 ± 10.4 s in the control group) and the duration of its manifestation (31.5 ± 5.6 s against 51, 2 ± 9.6 s in the control group); the tendency to weaken generation and storage of

short-term memory (STM): 50% and 33% instead of 83% and 67% in the control group (Fig. 3).

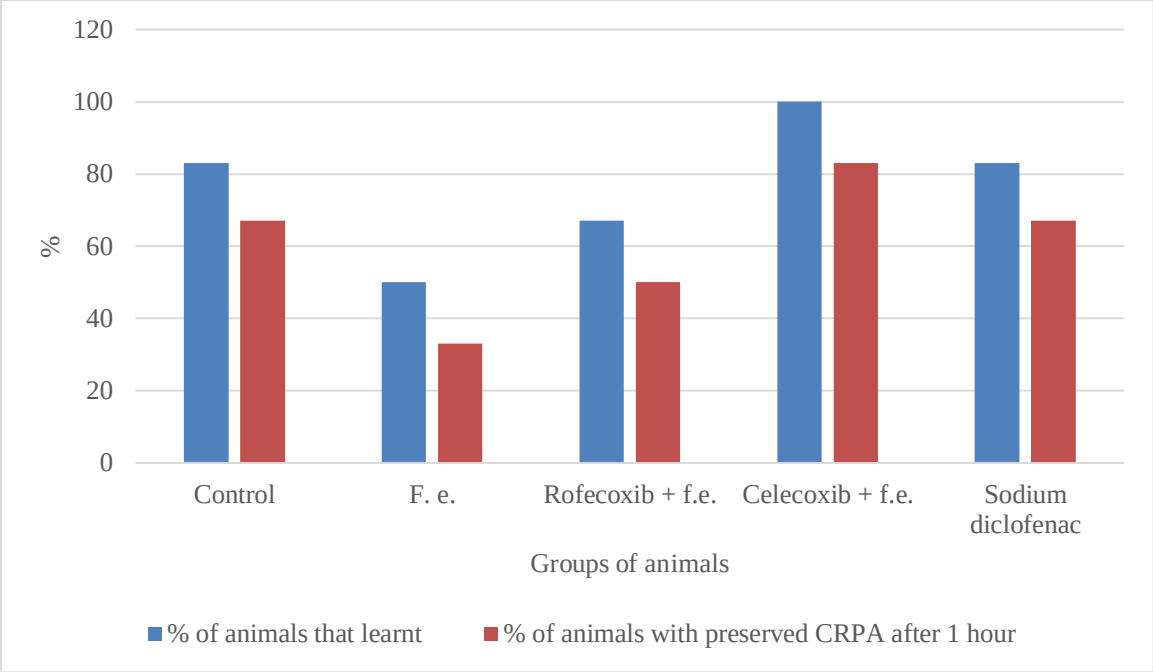

Fig. 3. Effect of coxibs on CRPA of laboratory rats (n = 6)

Rofecoxib under conditions of f. e. statistically significantly reduced the latent period of the reflex (36.2 ± 6.0 s) and its duration (15.3 ± 3.2 s), both against the control group and against the group with f. e., which approximated it according to the obtained indicators to diclofenac sodium (45.2 ± 3.2 s and 12.3 ± 4.0 s respectively).

Celecoxib under similar conditions statistically significantly increased the latency period of the reflex (82.6 ± 23.5 s), that is, it acts slowly and decreased its duration by 5.0 ± 1.7 s relative to the control groups (group 1) and f. e. (group 2).

The comparative analysis of the effect of the studied coxibs on the process of STM generation and preservation proves the priority position of celecoxib (100.0% and 83.0%, respectively), both in comparison with the reference drug (83.0% and 67.0%) and in comparison, with the reference rofecoxib (67.0% and 50%).

Conclusions.

1. The effect of NSAID coxibs (rofecoxib and celecoxib) on mnestic activity of rodents under conditions of f. e. was studied through the experiment.

2. The studied coxibs – celecoxib and rofecoxib – have a positive effect on mnestic activity of rats both by types of STM generation and its preservation.

3. Comparative analysis shows that celecoxib is recognized as the leader among the studied coxibs, the effectiveness of which exceeds both rofecoxib and the reference medicine from NSAID group – sodium diclofenac.

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