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EXPERIMENTAL STUDY OF RECEPTOR ANTAGONIST INTERLEUKIN-1 CEREBROPROTECTIVE PROPERTIES

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Abstract

In modern conditions craniocerebral trauma (CCT) is one of the most common pathologies. The search for new means of correcting CCT is an urgent task of medicine and pharmacy. According to the modern concept, the pathogenesis of brain lesions involves an increase in the production of pro-inflammatory cytokines, including interleukin-1. Attracts attention of the possibility to solve this problem by blockade of receptors of interleukin-1 (IL-1).

The aim of this study was to evaluate the effectiveness of raleukin in traumatic CNS lesions in a model of traumatic brain injury in rats.

Materials and methods. Raleukin injected at a dose of 15 mg / kg subcutaneously, referent-drug Piracetam (200 mg / kg) intraperitoneally 30 minutes before the modeling of CCT. Closed trauma of moderate severity was simulated under light etheric anesthesia (immediately after the lateral position of the animal) by the method of dosed impact on the parieto-occipital region with a weight of 0.0495 kg with an energy of 0.315 J in a special device. Immediately after the application of CCT determined the time of recovery of motor activity of animals. After 24 hours, the open field and rotating rod tests were repeated. This allowed us to assess the dynamics of the CNS.

The main results. In the article are the results of studies of the effect of recombinant human receptor antagonist of interleukin-1 (Raleukin) status of animals after closed craniocerebral trauma. Found that Raleukin more effective of piracetam restores motor activity of animals in the acute period of experimental BI. Against the background of Raleukin recovery in the functional state of central nervous system (muscle tone and motor coordination, motor and research activity, emotional reaction) in craniocerebral trauma rehabilitation period is better than under the influence of piracetam.

Key words: *interleukin-1, raleukin, craniocerebral trauma, cerebroprotective action*

Introduction

Today craniocerebral trauma (CCT) is one of the common pathological states. Its frequency ranges from 180 to 220 per 100 thousand population. With severe trauma up to 30-50% of patients die, and a significant proportion of survivors remain disabled [1, 2]. Existing treatment technologies are often ineffective. Therefore, the search for new means of correcting CCT is an urgent task of medicine and pharmacy [3, 4].

According to the modern concept, the pathogenesis of brain lesions involves an increase in the production of pro-inflammatory cytokines, including interleukin-1 (IL-1) [5, 6, 7, 8, 9]. It is proved that the production of interleukins, including IL-1, increases in various lesions of the brain, the rapid expression of which causes leukocyte infiltration, neurotoxicity, induces neuronal apoptosis [10, 11, 12]. Previous studies on ischemic cerebral circulatory disorders have shown strong cerebroprotective properties of a recombinant IL-1 receptor antagonist (Raleukin), namely increased survival, decreased cerebral edema and neurological deficits, and reduced cerebrovascular syndrome [13, 14, 15]. The aim of this study was to evaluate the effectiveness of raleukin in traumatic CNS lesions in a model of traumatic brain injury in rats.

Methods

The original recombinant antagonist of IL-1 receptors was obtained at the St. Petersburg Research Institute of Genetic Engineering by genetic engineering. The experiment was performed on 18 white outbred male rats weighing 150-230 g. Animals were divided into 3 groups of 6 individuals each. The first group - control pathology (received isotonic NaCl solution). The rats of the second group were injected Raleukin at a dose of 15 mg / kg subcutaneously 30 minutes before the simulation of CCT, which was determined in previous studies [16]. Animals of the third group 30 minutes before the simulation of CCT the comparison drug Piracetam (200 mg / kg) intraperitoneally administered.

1 hour before TBI simulation in rats, the initial functional state of the CNS was determined by open field and rod tests rotating at a speed of 10 revolutions per minute. This allowed to quantify the locomotor and research activity of animals, emotional reactions and their autonomic support, the state of muscle tone and coordination of movements.

Closed trauma of moderate severity was simulated under light etheric anesthesia (immediately after the lateral position of the animal) by the method of dosed impact on the parieto-occipital region with a weight of 0.0495 kg with an energy of 0.315 J in a special device [17, 18]. Immediately after the application of CCT determined the time of recovery of motor activity of animals. After 24 hours, the open field and rotating rod tests were repeated. This allowed us to assess the dynamics of the CNS.

Quantitative data were statistically processed using Student's t test, Wilcoxon pair test, and Fisher's angular transformation.

Results and Discussion

Moderate CCT did not cause animal death. According to Table 1, the restoration of motor activity occurred in different groups differently. Against the background of Raleukin, the onset of spontaneous movements and complete recovery of locomotor activity was observed significantly earlier than in the control pathology or piracetam groups. In addition, piracetam almost did not accelerate this process.

Under the influence of CCT in all groups, the results of the open field test deteriorated (Table 2). These indicators characterize the horizontal and vertical components of motor activity (respectively, the number of crossed squares and vertical racks), research activity (number of examined holes), manifestations of emotionality (grooming) and autonomic support of emotional reactions (defecation and urination). The largest violations were observed in the group of control pathology, the smallest - in the group of Raleukin. Thus, the sum of all types of activity in the control decreased by an average of 71.8% from baseline, under the influence of piracetam - by 56.6%, under the action of Raleukin - only by 24.0% (Table 2). These data suggest that raleukin corrects neurological deficits caused by trauma better than Piracetam.

The dynamics of muscle tone and coordination were also different. As can be seen from table. 3, in

the control pathology group and on the background of piracetam, the number of rats that did not stay on the rod after trauma was maximum and had no significant differences between them. Under the influence of Raleukin 24 hours after trauma, all animals remained on the rod for more than 30 s, which is probably higher than the control group and indicates the preservation of normal muscle tone and coordination.

Therefore, in the model of CCT of moderate severity in rats in the prophylactic administration of Raleukin had a positive effect on the recovery period of animals, exceeding the known nootropic and cerebroprotective agent piracetam. This is evidenced by a much faster recovery of motor activity after trauma, less suppression of motor and research activity on the open field test the day after trauma and the lack of suppression of emotional reactions in this test. In addition, raleukin, in contrast to piracetam, slightly improved muscle tone and coordination in the rotating rod test. These results indicate the prospects of blockade of IL-1 receptors as one of the mechanisms of cerebroprotection in traumatic brain injury [19, 20]. The cerebroprotective effect of raleukin is likely to be due to improved blood supply to the brain and its energy and plastic metabolism, a positive effect on neurotransmitter processes, anti-edematous activity, inhibition of apoptosis [21]. Verification of these mechanisms is the task of further studies of the cerebroprotective effect of Raleukin. It should be noted that according to previous studies, Raleukin reduces the depressant effect of alcohol on the CNS, which is important in the context of this study, as most cases of trauma occur in a state of alcohol intoxication [22].

Thus, Raleukin significantly outweighs the comparison drug with a positive effect on motor activity of experimental animals in the most acute period of experimental trauma, as well as on the restoration of functional CNS (muscle tone and coordination, motor and research activity, emotional reactions) in the rehabilitation period of CCT.

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Table 1. Time of recovery of motor activity after trauma simulation under the influence of Raleukin

Group (n=6)	Time of recovery of motor activity, sec	
	Start	Complete recovery
Control pathology (CCT)	204,0±46,9	360,0±69,0
Raleukin + CCT	29,2±6,5*#	85,8±12,9*#
Piracetam + CCT	196,0±39,4	335,0±72,3

Note. Probable differences by Student's criterion (p<0,05): * – with control pathology, # – with group of piracetam.

Table 2. Open field test results (3 min.) before and 24 hours after modeling of CCT under the influence of Raleukin (n = 6)

Indicator		Control pathology (CCT)	Raleukin + CCT	Piracetam + CCT
Number of crossed squares	to	14,2±4,2	25,0±2,6	20,3±8,1
	after	3,5±2,2*	19,3±3,5*	7,3±3,8*
	changes,%	–75,4	–22,8	–63,9
Number of vertical racks	to	3,0±1,6	9,2±0,8	4,0±1,5
	after	1,0±0,3	5,7±2,1*	2,2±1,3*
	changes,%	–66,7	–38,0	–46,0
Number of surveyed holes	to	8,3±2,2	7,0±0,6	7,2±2,6
	after	2,0±0,8*	4,5±1,0*	3,5±1,3*
	changes,%	–76,0	–35,7	–51,1
Number of acts grooming	to	1,0±0,3	2,0±0,2	1,0±0,3
	after	0,7±0,3	2,2±0,6	0,7±0,3
	changes,%	–33,0	+10	–33,0
Number of fecal bolus	to	0,8±0,3	0,5±0,3	1,2±0,3
	after	0,5±0,3	1,0±0,5	0,8±0,2
	changes,%	–39,8	+100	–29,1
Number of urination	to	0,5±0,2	0,2±0,2	0,2±0,2
	after	0,2±0,2	0,3±0,2	0,2±0,2
	changes,%	–66,0	+50,0	±0
Sum of all kinds activity	to	27,8±7,7	43,8±4,8	33,8±8,0
	after	7,8±2,6*	33,3±5,8*	14,7±6,3*
	changes,%	–71,8	–24,0	–56,6

Note. * - probable differences with the initial state according to the paired Wilcoxon test (p<0,05).

Table 3. Effect of Raleukin on muscle tone and coordination in traumatic trauma rats by the rotating rod test (n=6)

The number of animals that did not hold on to the rod		Control pathology (CCT)	Raleukin + CCT	Piracetam + CCT
The initial state	to 30 sec.	0/6 (0%)	0/6 (0%)	1/6 (16,7%)
	to 1 min.	3/6 (50%)	0/6 (0%) * #	3/6 (50%)
In 24 hours after trauma	to 30 sec.	3/6 (50%)	0/6 (0%) * #	2/6 (33,3%)
	to 1 min.	3/6 (50%)	2/6 (33,3%)	4/6 (66,7%)

Note. * - probable differences with the control pathology ($p < 0.01$), # - with piracetam ($p < 0.05$) by Fisher's angular transformation.