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THE EFFECT OF PARACETAMOL AND CELECOXIB ON THE STATE OF HEMOCOAGULATION IN THE MOST ACUTE PERIOD OF HEAT INJURY IN RATS

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Ключові слова: *гостра теплова травма, інгібітори циклооксигенази, целекоксиб, парацетамол, зсідання крові*

Abstract. Effect of paracetamol and celecoxib on the state of hemocoagulation in the most acute period of heat injury in rats. Chuikova P.O., Shtrygol' S.Yu., Lebedinets I.O., Lytkin D.V. *Acute heat injury (AHI) occurs due to exposure to high environmental temperatures and is considered a dangerous condition that requires effective prevention and treatment. This underscores the importance of searching for and thoroughly studying thermoprotective agents. Previous studies on a rat model of AHI have shown that the highly selective cyclooxygenase-2 (COX-2) inhibitor celecoxib and the analgesic-antipyretic paracetamol effectively prevent hyperthermia, but celecoxib, unlike paracetamol, improves the functional state of the central nervous system during the recovery period. Since AHI induces blood coagulation disturbances, it is important to determine the effects of these thermoprotective agents on hemostasis. The aim of this study was to investigate the effects of paracetamol and celecoxib as effective thermoprotectors on coagulation parameters during the acute phase of heat trauma in rats. The AHI model was reproduced on adult white male rats through a 30-minute exposure to +55°C. The animals were divided into four groups of 7-8 rats each: intact control, pathological control, celecoxib group (8.4 mg/kg intragastrically 50-60 minutes before heat exposure), and paracetamol group (125 mg/kg in the same regimen). Rectal temperature was monitored, and in rat plasma, fibrinogen, prothrombin time (PT), thrombin time (TT), activated partial thromboplastin time (APTT) were determined, while D-dimer was measured in serum. The results showed that during the acute phase of AHI in the pathological control group, when body temperature increased by an average of 4.33±0.33°C ($p<0.01$ compared to baseline), fibrinogen, PT, TT, and APTT levels remained unchanged, but the D-dimer level in serum increased by 2.2 times, indicating enhanced thrombogenesis. Both celecoxib and paracetamol exhibited a statistically significant thermoprotective effect (temperature rise of 3.16±0.40°C and 3.21±0.12°C, respectively, $p<0.01$ compared to untreated animals), had no effect on fibrinogen, PT, TT, or APTT levels, but normalized the D-dimer level, indicating an antithrombotic effect. The results justify the use of COX inhibitors, particularly celecoxib, in AHI.*

Реферат. Вплив парацетамолу та целекоксибу на стан гемокоагуляції в найгострішому періоді теплової травми в щурів. Чуйкова П.О., Штриголь С.Ю., Лебединець І.О., Литкін Д.В. *Гостра теплова травма (ГТТ) виникає під впливом високої температури довкілля та належить до небезпечних станів, що потребують ефективної профілактики та лікування. Це зумовлює актуальність пошуку та різнобічного вивчення термопротекторних засобів. У попередніх дослідженнях на моделі ГТТ у щурів установлено, що високоселективний інгібітор циклооксигенази-2 (ЦОГ-2) целекоксиб та анальгетик-антипіретик парацетамол ефективно запобігають гіпертермії, проте целекоксиб, але не парацетамол поліпшує функціональний стан центральної нервової системи у відновному періоді. З огляду на ризик порушень зсідання крові за ГТТ доцільно з'ясувати вплив зазначених термопротекторних засобів на гемостаз. Метою цього дослідження стало з'ясування впливу парацетамолу та целекоксибу як ефективних термопротекторів на коагулологічні показники в найгострішому періоді перебігу теплової травми в щурів. Модель ГТТ відтворювали в дорослих білих щурів-самців шляхом 30-хвилинної експозиції за +55°С. Тварини були розподілені на 4 групи по 7-8 щурів у кожній: інтактний контроль, контрольна патологія, група целекоксибу (8,4 мг/кг інтрагастрально за 50-60 хв до теплової експозиції) та група парацетамолу (125 мг/кг в аналогічному режимі). Контролювали ректальну температуру щурів, у плазмі крові щурів визначали фібриноген, протромбіновий час (ПЧ), тромбіновий час (ТЧ), активований частковий протромбіновий час (АЧТЧ), у сироватці крові – D-димер. Результати показали, що в найгострішому періоді ГТТ щурів групи контрольної патології, коли температура тіла зростає в середньому на 4,33±0,33°С ($p<0,01$ щодо вихідного рівня), вміст фібриногену, ПЧ, ТЧ та АЧТЧ не зазнає достовірних змін, проте у 2,2 раза збільшується рівень D-димеру в сироватці крові, що вказує на посилене тромбоутворення. Як целекоксиб, так і парацетамол чинять статистично значущий термопро-*

текторний ефект (приріст температури становить відповідно 3,16±0,40°С та 3,21±0,12°С, p<0,01 щодо нелікованих тварин), не впливають на вміст фібриногену, ПЧ, ТЧ та АЧТЧ, але нормалізують рівень рівень D-димеру, що свідчить про антитромботичний вплив. Результати обґрунтовують доцільність застосування інгібіторів ЦОГ, насамперед целекоксибу, за ГТТ.

Acute heat injury (AHI) is a serious medical and social problem. Heat-related illnesses encompass a spectrum of syndromes that occur under the influence of elevated environmental temperatures, especially during intense physical exertion. This exposure can increase the risk of mortality from various diseases, including hypertension and other cardiovascular diseases, diabetes, etc. [1]. Due to several factors, such as climate change (global warming since the Industrial Revolution, high air humidity), the prevalence of military conflicts and man-made disasters, and working in hot conditions without air conditioning, the incidence of diseases associated with high environmental temperatures is increasing [2, 3]. Research [4] demonstrates an increase in mortality caused by increased global temperatures from 0.83% in 2000–2003 to 1.04% in 2016–2019. Globally, this corresponds to approximately 500,000 additional deaths each year from heat-related illnesses. Therefore, in-depth research into these conditions and methods of their prevention and treatment is needed.

During AHI, a stress response occurs, which leads to the release of catecholamines and glucocorticoids into the blood, circulatory disorders and the development of hypohydration, hypoxia, increased excretion of ions and water-soluble vitamins. As a result, in addition to the development of cardiovascular syndrome, blood viscosity increases, the hemocoagulation system is activated, the structure and functioning of proteins change, lipid peroxidation increases, which leads to the destruction of cell membranes, necrosis of cells and tissues, the release of cytokines with the development of a systemic inflammatory reaction, which causes a syndrome of multiple organ failure [5]. In particular, there are lesions of the central nervous system (CNS) with cerebral edema, severe disturbances of water-salt balance and internal organs, which can lead to coma and death [1].

The effectiveness of drugs for heat injuries has not been clinically proven, which emphasizes the importance of finding thermoprotectors with different mechanisms of action [6]. Since the inflammatory cascade associated with the metabolism of arachidonic acid plays an important role in the pathogenesis of heat injuries, cyclooxygenase (COX) inhibitors with different selectivity are potential candidates for the role of thermoprotectors. In previous studies on the model of acute heat injury (AHI) in rats, we found that the nonsteroidal anti-inflammatory drug (NSAID), a highly selective COX-2 inhibitor celecoxib, as well as the non-selective COX inhibitor analgesic-antipyretic paracetamol, demonstrate pronounced thermoprotective properties. Unlike a number of NSAIDs (acetylsalicylic acid, diclofenac sodium, nimesulide, etoricoxib), celecoxib and paracetamol statistically significantly reduce the degree of hyperthermia in rats with AHI, however, celecoxib is more effective than paracetamol in normalizing the functional state of the CNS [7, 8]. Therefore, the mere fact of preventing hyperthermia does not mean an equivalent beneficial effect of thermoprotectors on the state of organs and systems in AHI. Given the great importance of activation of the hemocoagulation system in the pathogenesis of AHI [5], a natural question arises regarding the effect of these agents on the state of hemostasis. The aim of the study is to determine the effect of paracetamol and celecoxib as effective thermoprotectors on coagulological parameters in the most acute period of thermal injury in rats.

MATERIALS AND METHODS OF RESEARCH

The experiment was performed on 30 white male rats weighing 250-300 g. The animals were kept in standard polypropylene cages at a temperature of 21-25°C and a relative humidity of 50% in ventilated rooms with a 12-hour day/night cycle and free access to food and water. All experiments were approved by the Bioethics Committee of the National University of Pharmacy (excerpt from the meeting protocol No. 12 dated January 10, 2024) and conducted in accordance with the requirements of the European Convention "For the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes" (Strasbourg, 1986, as amended in 1998), in compliance with the Law of Ukraine No. 3446–IV dated February 21, 2006, as amended "On the Protection of Animals from Cruelty" and the European Union Directive 2010/63 EU "On the Protection of Animals Used for Scientific Purposes." Paracetamol (Paracetamol, 500 mg capsules, "Zdorovia", Ukraine) and celecoxib (Celebrex, 200 mg capsules, "Pfizer", USA) were used in effective thermoprotective doses of 125 mg/kg and 8.4 mg/kg, respectively [7, 8].

AHI was simulated by 30-minute exposure of rats to +55°C [7]. Initial and final rectal temperatures were measured using an electronic thermometer Gamma Thermo Base. Rats were randomly divided into 4 groups: 1) intact control, n=8; 2) control pathology, n=7; 3) animals that were intragastrically (i.g.)

injected with paracetamol, n=8; 4) rats treated with celecoxib, n=7. The drugs were crushed, suspended with Tween-80 and administered via a probe i.g. in a volume of 0.5 ml per 100 g of body weight 50-60 min. before thermal injury modeling. Rats of the intact control and control pathology groups received i.g. drinking water in the same volume.

After the completion of the thermal exposure and final thermometry, the animals were anesthetized with sodium thiopental (40 mg/kg intraperitoneally), after 5-10 min. they were decapitated and blood samples were collected to obtain plasma and serum, in which coagulological parameters were determined. Prothrombin time (PT), thrombin time (TT), activated partial thromboplastin time (APTT), and fibrinogen were determined in blood plasma using kits manufactured by BioSystem S.A. (Spain). D-dimer was determined in serum by enzyme-linked immunosorbent assay (ELISA) using the species-specific Rat D-Dimer ELISA Kit (MyBioSource, USA) on a LAB Analyt M201 Microplate Reader.

The Statistica 10.0 licensed program (StatSoftInc., serial number STA999K347156-W) was used for statistical processing of the results. The hypothesis of normal data distribution was rejected using the Shapiro-Wilk test and the values of the coefficients of asymmetry and kurtosis [9]. The statistical significance of the differences was determined using the Kruskal-Wallis test with post hoc comparisons using the Mann-Whitney test, which allowed us to identify which groups had significant differences. Temperature changes within each group were assessed using the Wilcoxon paired test. Given the comparison of not 2, but 4 groups, to avoid the accidental detection of probable differences, the statistical significance criterion $p<0.017$ was chosen. The results are presented as arithmetic means with standard errors (M±m) and medians with 25% and 75% percentiles (Me [Q25; Q75]).

RESULTS AND DISCUSSION

The initial temperature of the rats was similar and ranged from 36.3 to 38.6°C, which corresponds to the physiological norm of this species of animals. After heat exposure, hyperthermia was observed in all rats, especially pronounced in the control pathology group (average temperature increase of 4.33°C). Both celecoxib and paracetamol significantly reduced the severity of hyperthermia compared to the control pathology (average temperature increase was 3.16°C and 3.21°C, respectively (Table 1).

Table 1

The effect of paracetamol and celecoxib on the rectal temperature of rats with an acute heat injury model (M±m, Me[Q25; Q75])

Group, number of animals	Rectal temperature, °C		Overall increase, °C
	initial	at 30 min of heat exposure	
Intact control (n=8)	**37.63±0.18** **37.6 [37.4; 37.7]**	–	–
	Acute heat injury		
Control pathology (n=7)	**36.84±0.13** **37.0 [36.7; 37.1]**	**41.17±0.39*** **40.8 [40.7; 41.5]**	**4.33±0.33** **4.0 [3.8; 4.7]**
Paracetamol (n=8)	**36.91±0.12** **36.9 [36.7; 37.2]**	**40.13±0.15*** **40.1 [39.8; 40.2]**	**3.21±0.12#** **3.2 [3.0; 3.4]**
Celecoxib (n=7)	**37.56±0.30** **37.4 [37.1; 38.1]**	**40.71±0.15*** **40.6 [40.4; 41.1]**	**3.16±0.40#** **3.6 [2.4; 3.9]**

Notes: n – number of animals in the group; * – significant differences from the baseline, $p<0.01$; # – significant differences from the control pathology group, $p<0.01$.

Most of the coagulation markers in the blood plasma (PT, TT, APTT, fibrinogen) were almost unchanged. There was a statistically insignificant increase in fibrinogen content in animals of the control pathology and the paracetamol group. There was also a tendency to increase in TT in the control pathology group, but not under the influence of celecoxib or paracetamol (Table 2).

Table 2

The effect of paracetamol and celecoxib on coagulogram parameters and D-dimer content in the blood of rats in the most acute period of thermal injury (M±m, Me[Q25; Q75])

Markers	Intact control (n=8)	Acute heat injury		
		control pathology (n=7)	paracetamol (n=8)	celecoxib (n=7)
Blood plasma				
Fibrinogen, g/l	3.68±0.45 4.1 [2.9; 4.5]	4.11±0.47 4.4 [3.6; 4.8]	4.43±0.28 4.7 [4.2; 5.0]	3.86±0.65 3.3 [3.1; 4.5]
Prothrombin time, s	13.10±0.26 13.1 [12.9; 13.7]	13.40±0.62 12.9 [12.6; 13.7]	13.73±0.21 13.7 [13.5; 14.0]	14.49±1.00 14.6 [14.0; 15.5]
Thrombin time, s	53.31±5.61 48.5 [45.4; 52.6]	57.29±5.08 56.7 [47.1; 66.6]	49.14±1.14 49.0 [48.3; 49.8]	52.10±10.71 48.1 [45.6; 63.1]
APTT, s	29.78±2.15 29.1 [26.1; 34.7]	27.36±2.69 24.5 [23.0; 32.5]	26.45±1.68 26.5 [23.2; 29.8]	33.63±3.90 27.5 [26.8; 41.8]
Blood serum				
D-dimer, ng/ml	6.39±0.92 6.3 [4.5; 7.3]	14.24±1.65$^{\&\&}$ 14.7 [10.9; 16.6]	7.36±0.79* 7.1 [6.2; 8.4]	6.15±0.90** 7.4 [4.4; 7.7]

Notes: n – number of animals in the group; $^{\&\&}$ – p<0.001 relative to intact control; * – p<0.01, ** – p<0.001 relative to control pathology.

However, it is noteworthy that there was a significant (2.2-fold) increase in the D-dimer content in the blood serum of rats in the control pathology group (p<0.001). Against the background of both drugs, this increase does not occur. At the same time, in the paracetamol group, the D-dimer level was tending to be higher than in intact animals but lower compared to the control pathology (p<0.01). Against the background of celecoxib, the D-dimer content practically does not differ from the intact control and is significantly lower than in the control pathology group (p<0.001).

The body temperature of rats exposed to heat under the influence of both drugs increased to a much lesser extent than in animals of the control pathology group. In previous studies on the AHI model under the influence of celecoxib and paracetamol, similar results were observed, and the minimum degree of hyperthermia occurred against the background of the highly selective COX inhibitor celecoxib, which confirms its pronounced thermoprotective effect [7, 8]. The results of this experiment correspond to the data of the cited studies.

Under the influence of stress-realizing factors, such as the influence of high environmental temperature, the systemic inflammatory process is activated, which can lead to damage to the vascular endothelium and impaired hemostasis with increased thrombus formation. Hyperthermia causes stimulation of platelets and endothelial cells with the release of procoagulant factors that contribute to increased blood clotting [10]. The results of our study confirm these data and indicate that already in the most acute period of thermal injury in rats of the control pathology group, increased thrombus formation occurs, which may be a manifestation of acute disseminated intravascular coagulation (DIC) syndrome. This is directly indicated by a significant (by 122%) increase in the level of D-dimer in the blood serum, which is an informative marker of thrombus formation [11]. This is also consistent with the trend of an increase in TT in the control pathology group. TT characterizes the transformation of fibrinogen into fibrin – the final stage of the blood coagulation cascade. The tendency to increase this indicator in animals with AHI can be explained precisely by the presence of fibrin degradation products in the blood, which is indicated by a high content of D-dimer [11]. At the same time, the fibrinogen level in blood plasma, which tends to increase by 11.7%, may be associated with a short time of exposure to high temperature, during which a significant increase in this component of the hemocoagulation system does not have time to occur. For further clarification, coagulological studies are required not only in the most acute period of AHI, but also in the dynamics of the post-hyperthermic state.

When discussing the content of D-dimer in the blood of rats, it is advisable to compare the obtained results with reference values. Literature analysis

shows that this indicator can fluctuate widely depending on the rat line, method of determination, etc. In a thorough review [12], covering 60 valid publications for 2000-2019, mean values for intact rats ranged from 0.18 to 500 ng/ml (using human ELISA kit, 26 publications); from 0.05 to 19.6 ng/ml (using species-specific rat ELISA kit, 4 publications); from 0.03 to 350 ng/ml (automated assay, 28 publications) and from 32 to 250 ng/ml (manual turbidimetric assay, 2 publications). Our results (6.39±0.92 ng/ml in intact control) correspond well to the values obtained using ELISA kits for rats, which emphasizes the importance of using species-specific reagents.

The question arises as to the reason for the increase in D-dimer content in the serum of rats with the AHI model. This small protein fragment is a product of fibrinolysis, the destruction of a thrombus. D-dimer is formed by the cleavage of insoluble fibrin by plasmin. It is considered primarily a marker of increased hemocoagulation and thrombosis [13]. It has been proven that heat stroke is characterized by cell damage, hyperinflammation, and hypercoagulability with suppressed fibrinolysis, leading to coagulopathy that can progress to disseminated intravascular coagulation and multiple organ failure [5, 14]. D-dimer, as well as platelet count, soluble thrombomodulin, and inflammatory biomarkers such as interleukin-6, are considered promising markers for AHI [14]. Therefore, the increase in D-dimer detected in our study should be regarded as an indicator of hypercoagulability and increased thrombus formation. Both paracetamol and celecoxib significantly reduce the adverse shift in hemocoagulation in the most acute period of heat injury. Under the influence of each of these agents, no significant changes occur in the PT, TT, APTT, and fibrinogen content in blood plasma. The decrease in serum D-dimer content compared to the control pathology group, especially pronounced under the influence of celecoxib, indicates a decrease in the risk of thrombosis and DIC syndrome in AHI. The similar antithrombotic effect of both studied agents does not allow to explain the slightly higher thermoprotective efficacy of celecoxib compared to paracetamol and the previously revealed more pronounced neuroprotective properties of the highly selective COX-2 inhibitor [8] from the position of greater inhibition of thrombus formation and improvement of hemorheological properties. Obviously, a complex of mechanisms is important, the severity of each of which may differ in each drug. However, it is important that already at an early stage of AHI, both celecoxib and paracetamol prevent increased thrombus formation, which is important for a favorable course of the recovery period, and do not cause bleeding.

The effect of COX inhibitors on hemostasis consists of effects on its platelet and the coagulation link studied by us. Obviously, this effect may depend on the initial state of the organism. Our study concerns a specific pathology – thermal injury, and it is not possible to fully compare the results obtained with the data of other authors. However, information on the effect of the studied COX inhibitors on thrombus formation is quite contradictory. Thus, celecoxib usually does not have a significant effect on hemostasis, because it selectively inhibits COX-2, not COX-1. It is COX-1 that is mainly responsible for the mechanisms of blood clotting and platelet aggregation. As shown by the analysis of the course of the disease in more than 108 thousand patients who suffered an acute myocardial infarction, when using 8 different NSAIDs, the risk of developing cardiovascular events and bleeding was the lowest in the case of celecoxib [15]. A meta-analysis of 35 studies on the risk of perioperative bleeding showed that highly selective COX-2 inhibitors do not significantly increase the risk of intraoperative or postoperative bleeding, and do not have a significant effect on the functional state of platelets [16]. The conclusion of the authors of the cited review is that a single perioperative use or a short course of COX-2 inhibitors (in particular, celecoxib) in surgical patients is safe. The risk of bleeding with celecoxib is slightly increased in patients taking this COX-2 inhibitor and the indirect anticoagulant warfarin simultaneously compared with those taking warfarin alone: during 1063 months of use of these two agents, only 10 cases of bleeding were detected in 123 patients, one of which was serious [17]. However, deep vein thrombosis caused by celecoxib is also known [18], although the prothrombogenic property of highly selective COX-2 inhibitors is mostly inherent to rofecoxib and concerns arterial, but not venous thrombosis [19] and is not considered specific for this group of drugs.

Paracetamol, as a moderate COX-1 inhibitor with predominantly central action, has little effect on both platelet and coagulation hemostasis in therapeutic doses [20]. However, there are reports that this drug is able to inhibit arachidonic acid and collagen-stimulated human platelet aggregation without significant effects on the PT and APTT [21]. In high (hepatotoxic) doses, paracetamol activates the coagulation cascade in vivo and suppresses it ex vivo. In particular, this effect was observed in mice with a model of hepatotoxicity and acute liver failure, which was induced by paracetamol at doses of 300-600 mg/kg [22].

It is possible that the reduction in thrombus formation under the influence of celecoxib and paracetamol in rats with AHI, detected in our experiment, is of a non-specific secondary nature and is associated

with a decrease in hyperthermia. However, it is obvious that this effect has a beneficial meaning. In further studies, it is advisable to clarify the effect of the most effective thermoprotective agents not only on the coagulation, but also on the platelet side of hemostasis, as well as the subtle mechanisms of their action. According to AHI, based on the combination of known features of thermoprotective properties of the most effective COX-inhibiting agents, celecoxib has advantages over paracetamol, as it not only thrombus formation, but also normalizes the impaired functional state of the CNS [8].

CONCLUSIONS

1. Celecoxib (8.4 mg/kg) and paracetamol (125 mg/kg) reduce the degree of hyperthermia in acute heat injury caused by 30-minute exposure of rats at +55°C.
2. In the most acute period of heat injury (immediately after heat exposure), rats in the control pathology group have a significant increase in serum D-dimer, indicating an increased risk of thrombosis and the development of disseminated intravascular coagulation (DIC) syndrome.
3. Paracetamol statistically significantly reduces, while celecoxib completely normalizes the content of D-dimer, indicating an antithrombotic effect in the most acute period of heat injury.

Recommendations. In studies of thermoprotective agents, it is advisable to determine the effect on hemostasis.

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Contributions:

Chuykova P.O. – investigation, writing – original draft;

Shtrygol' S.Yu. – conceptualization, methodology, investigation, writing – review and editing;

Lebedynets I.O. – investigation;

Lytkin D.V. – investigation.

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