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Метаболит N-ацетил-парабензохинонимин как фактор возможной нейротоксичности парацетамола

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Обоснование. В современной научной литературе широко обсуждают возможное негативное влияние парацетамола на центральную нервную систему, в частности, связь его приема во время беременности с риском возникновения расстройств аутистического спектра у ребенка. Однако есть много вопросов к методам оценки нарушений поведения и обработке результатов исследований по этой теме. Поэтому экспериментальные данные, полученные на нейрональных клетках, могут стать достаточным основанием, чтобы подтвердить или опровергнуть предположения о нейротоксичности парацетамола и его метаболитов.

Цель исследования — изучить влияние парацетамола и его метаболита N-ацетил-парабензохинонимина (NAPQI) на нейроны коры мозга плодов крыс.

Материалы и методы. Исследование влияния парацетамола и его метаболита на жизнеспособность клеток проведено методом, основанным на восстановлении бромиды 3-(4,5-диметилтиазол-2-ил)-2,5-тетразолия (МТТ).

Результаты. При преинкубации нейронов коры мозга крыс с парацетамолом в концентрации 1 мг/мл в течение 24 ч и последующей инкубацией с 0,3 мМ перекисью водорода установлено влияние этих веществ на снижение жизнеспособности нейронов, в том числе при инкубации с ними обоими. Тот же эффект обнаружен при совместной преинкубации с парацетамолом или его метаболитом и перекисью водорода.

Выводы. Как парацетамол, так и его метаболит NAPQI снижают жизнеспособность нейронов коры плодов крыс.

Ключевые слова: нейроны; линия PC12; парацетамол; NAPQI.

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N-acetyl-p-benzoquinonimine metabolite as a factor of possible neurotoxicity of paracetamol

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BACKGROUND: Currently, the possible negative effects of paracetamol on the central nervous system are widely discussed in the modern scientific literature. The relationship between the intake of paracetamol during pregnancy by women and the risk of autism spectrum disorders in their children is being studied. However, such conclusions are often met with serious criticism as there are many questions about the methods of assessing behavioral disorders and processing research results. Therefore, experimental data obtained on neuronal cells may be a sufficient ground to confirm or refute assumptions about the neurotoxicity of paracetamol and its metabolites.

AIM: To study the effect of paracetamol and its metabolite N-acetyl-p-benzoquinonimine (NAPQI) on the neurons of the cerebral cortex of fetal rats.

MATERIALS AND METHODS: The study of the effect of paracetamol and its metabolite NAPQI on cell viability has been carried out by a method based on the reduction of 3-(4,5-dimethylthiazole-2-yl)-2,5-tetrazolium bromide (MTT).

RESULTS: It has been shown that during preincubation of neurons in the cerebral cortex of the rats with paracetamol at a concentration of 1 mg/ml for 24 hours and subsequent incubation with 0.3 mM hydrogen peroxide, both hydrogen peroxide and paracetamol itself reduce the viability of neurons. Joint incubation with paracetamol and hydrogen peroxide also reduces the viability of neurons. The same effect of paracetamol and its metabolite is observed with the joint preincubation of paracetamol or NAPQI and hydrogen peroxide.

CONCLUSIONS: Paracetamol as well its metabolite NAPQI reduce the viability of neurons in the fetal cortex of rats.

Keywords: neurons; PC12 line; paracetamol; NAPQI.

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BACKGROUND

Paracetamol (acetaminophen) is the most common anti-pyretic and analgesic drug that, to a lesser extent than most nonsteroidal anti-inflammatory drugs, is characterized by side effects in the form of damage to the gastrointestinal tract, increased systemic vascular resistance with kidney damage, and fluid retention due to impaired synthesis of prostaglandins. Due to its popularity and perceived high level of safety, paracetamol is used during pregnancy. In the United States, it is used by 25%–40% of pregnant women, and 3%–20% of them take it during all three trimesters [1]. However, paracetamol is hepatotoxic when overdosed and is estimated to be the most common cause of liver failure in the United States and Europe. In 44% of healthy volunteers, a single dose of paracetamol caused an increase in hepatic transaminases [2].

The toxicity of paracetamol is based on its metabolism (Fig. 1), the minor pathway of which leads to the formation of N-acetyl-parabenzquinoneimine (NAPQI).

With normal paracetamol intake, this metabolite is harmless, as it is rapidly conjugated by glutathione S-transferase and excreted in the bile. Its covalent association with sulfhydryl groups of proteins rarely occurs with the formation of stable protein adducts that are normally removed by autophagy [3]. NAPQI is accumulated when high doses of paracetamol are taken, and the saturation limit is subsequently achieved. In this case, mitochondrial proteins are converted into irreversibly formed nonfunctional conjugates, glutathione deficiency occurs, an oxidative stress reaction develops, and apoptosis is triggered [4]. Predisposing factors to the toxic effects of paracetamol are exhaustion, prolonged diet (depletion of glutathione reserves), alcohol consumption (induction of metabolism in the CYP2E1 system), and a decrease in the content of bile acids that restore hepatocytes [5].

The toxicity mechanisms, described in detail, associated with paracetamol metabolism, together with its popularity in pregnant women, are of concern. NAPQI formation depends on enzymes whose activity increases during pregnancy [6],

namely, cytochromes of CYP2A6, CYP3A4, and CYP2D6 families. At the same time, it cannot be ruled out that NAPQI toxicity poses a threat to the developing fetal nervous system that is vulnerable to external factors. Studies have shown an association between the use of paracetamol by the mother during pregnancy and behavioral disorders in older children [7]. The toxicity of paracetamol and NAPQI for nervous system cells was analyzed in an experiment.

This study aimed to analyze the effects of the paracetamol metabolite NAPQI on rat cerebral cortex neurons under oxidative stress induced by hydrogen peroxide (H_2O_2).

MATERIALS AND METHODS

H_2O_2 , paracetamol, cytosine- β -D-arabinofuranoside, poly-D-lysine (Sigma, USA), Dulbecco's modified Eagle's medium (DMEM) with L-glutamine, fetal bovine serum, trypsin, penicillin, and streptomycin (BioLT, Russia) were used for the study.

Neurons were isolated from the cerebral cortex of rat embryos on days 17 and 18 of development [8]. Trypsin was used to isolate cells, and cytosine- β -D-arabinofuranoside was used to prevent glial cell proliferation. Neurons were grown in complete DMEM containing 10% F-12 medium, 10% fetal bovine serum, 2 mM L-glutamine, and 20 mM HEPES. Neuronal cells were inoculated into a complete growth medium in 96-well plates coated with poly-D-lysine at 4×10^5 per well. The next day, cells were treated with 1 μ M cytosine- β -D-arabinofuranoside, which was replaced with complete growth medium after 24 h. Experiments started on days 5 and 6 of cell cultivation *in vitro*.

Cell viability was determined by a method based on the reduction of 3-(4,5-dimethylthiazol-2-yl)-2,5-tetrazolium bromide (MTT) [9]. Cells were inoculated in a 96-well plate at 5×10^4 per well. After 24 h, the complete growth medium was changed to DMEM with L-glutamine. Cells were incubated with paracetamol (1 mg/ml) or NAPQI (0.1 mg/ml) for 24 h. H_2O_2 (0.3 mM) was added 2.5 h before the termination of

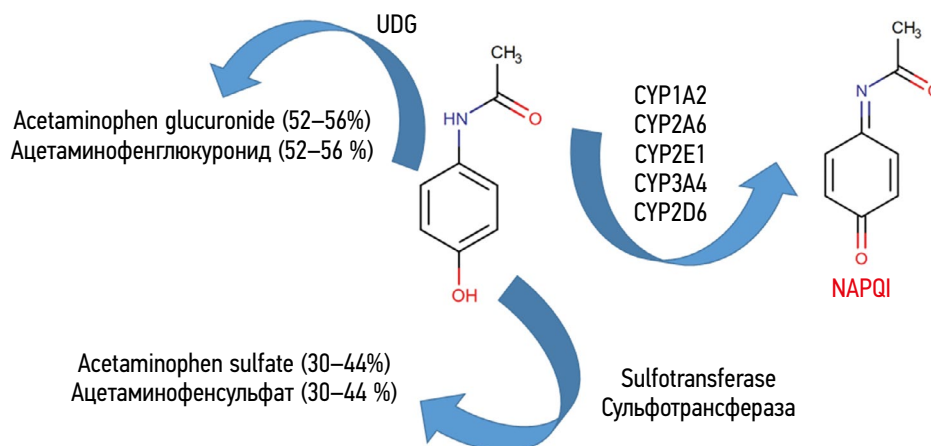


Fig. 1. Metabolism of paracetamol. NAPQI — N-acetyl-p-benzoquinoneimine; UDG — uridine-diphosphate (UDG)-glucuronosyl transferase
Рис. 1. Метаболизм парацетамола. NAPQI — N-ацетил-парабензохинонимин; UDG — УДФ-глюкуронилтрансфераза

incubation. The MTT reagent (0.5 mg/ml) was added 2 h before the termination of incubation. After 2 h, cells were lysed with 20% sodium dodecyl sulfate in 50% dimethylformamide in 0.05 N HCl. The content of the stained reaction product (MTT-formazan) was measured by determining the optical density at 570 nm on a microplate reader. The results were expressed as a percentage of the control values, namely conditional 100% MTT-formazan in PC12 cells not exposed to paracetamol, NAPQI, and H₂O₂.

Changes in the mitochondrial membrane potential (MMP) were verified by flow cytometry using the cationic stain JC-1. Cells were incubated with paracetamol (1 mg/ml) or NAPQI (0.1 mg/ml) for 24 h. One hour before the end of incubation, H₂O₂ (0.3 mM) was added. The JC-1 stain was added to the final concentration 0.5 h before the end of the incubation. Measurements were performed on an FC-500 flow cytometer (Beckman Coulter) at FL1 of 525 ± 40 nm, FL2 of 575 ± 30 nm, and λ_{ex} of 488 nm. The color change from red to green was evaluated and quantified. The results were expressed as a percentage of the control values associated with PC12 cells not exposed to the substances studied.

RESULTS AND DISCUSSION

Figure 2 presents the results of one of three typical experiments. Preincubation with H₂O₂ (0.3 mM), paracetamol (1 mg/ml), and NAPQI (0.1 mg/ml) reduced the percentage of surviving cells to 51.5%, 85.2%, and 85.6%, respectively. Coincubation with H₂O₂ and paracetamol or NAPQI revealed an even more significant decrease in the viability of neurons (up to 52.8%) than in control cells.

This preincubation also reduced the MMP to 90.0%, 90.7%, and 90.5%, respectively (Fig. 3). Coincubation with H₂O₂ and paracetamol or NAPQI revealed an even greater decrease in the MMP to 88.9% and 80.6%, respectively, than in control cells.

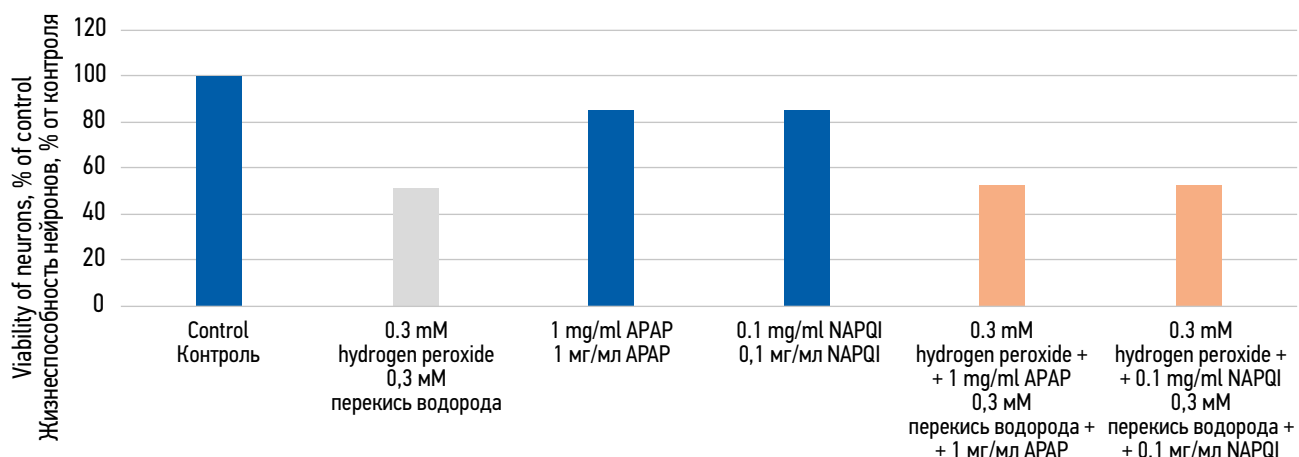


Fig. 2. The effect of paracetamol and NAPQI on the survival of neurons in the cerebral cortex of the fetal rats. APAP — paracetamol; NAPQI — N-acetyl-p-benzoquinonimine

Рис. 2. Влияние парацетамола и N-ацетил-парабензохинонимина на выживание нейронов коры мозга плодов крыс. APAP — парацетамол; NAPQI — N-ацетил-парабензохинонимин

The effects of paracetamol on fetal brain development remain a matter of debate. The Danish National Birth Registry revealed an association between paracetamol intake by pregnant women and autism spectrum disorders in their children [10]. Similar results were found in other cohorts, namely, the Norwegian MoBa cohort [11] and the Nurses' Health Study cohort, one of the largest registries that study women's health [12]. A meta-analysis of published studies confirmed the relationship between paracetamol use in pregnant women and the risk of attention-deficit hyperactivity disorder in children [13].

Measurement of paracetamol concentrations and its metabolite when identifying associations is difficult due to the heterogeneity of the study results. The drug dose considered safe for use during pregnancy remains unclear [14].

There is not much information from animal experiments. C. Rigobello et al. found that pups of pregnant rats given paracetamol showed signs of social maladjustment, cognitive impairment, and impairment of metabolism of monoamines in the hypothalamus, cerebellum, and spinal cord at age 2 months [15].

Experiments have shown that paracetamol can significantly increase the expression of JNK, HIF1A, and CASP3, which are the markers of cell apoptosis in human glioblastoma A172 spheroids [16]. At 1 and 2 mM, paracetamol increases neuronal line PC12 cell death [17, 18].

There is also evidence that paracetamol causes cognitive impairment and changes in the amount of neurotrophic factors in different parts of the brain (an increase in the frontal cortex and a decrease in the temporal lobe) in mice [19].

CONCLUSION

Previously, paracetamol was shown to have a toxic effect on the neuronal line PC12 [9, 17, 18]. The findings that paracetamol and its metabolite NAPQI reduce the viability and MMP of neurons in the cerebral cortex of rat fetuses

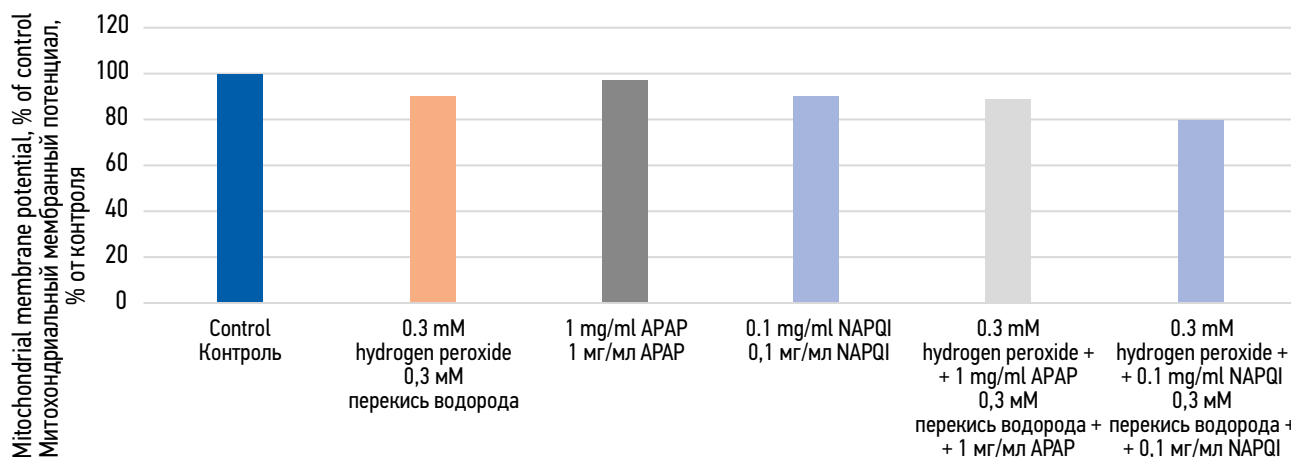


Fig. 3. The effect of paracetamol and NAPQI on the change in the mitochondrial membrane potential of neurons in the cerebral cortex of the fetal rats. APAP — paracetamol; NAPQI — N-acetyl-p-benzoquinonimine

Рис. 3. Влияние парацетамола и N-ацетил-парабензохинонимина на изменение митохондриального мембранного потенциала в нейронах коры мозга плодов крыс. APAP — парацетамол; NAPQI — N-ацетил-парабензохинонимин

may indicate a possible toxic effect of this drug on nervous tissue. This research contributed to the biological mechanism that may explain the neurotoxic effects of paracetamol, particularly on the developing fetal brain. It is necessary to study the aspects of NAPQI formation associated with changes in CYP2D6 and CYP3A4 activity during pregnancy. It is believed that the most difficult task is to determine the critical dose and period of paracetamol use during pregnancy, which is essential for the implementation of its neurotoxicity.

ADDITIONAL INFORMATION

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All authors made a significant contribution to the study and preparation of the article and read and approved the final version before its publication.

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