УДК 612.8.015:576.345
DOI: https://doi.org/10.17816/mechnikov99620

Метаболит N-ацетил-парабензохинонимин как фактор возможной нейротоксичности парацетамола

Ю.А. Власова, К.А. Загородникова

Северо-Западный государственный медицинский университет им. И.И. Мечникова, Санкт-Петербург, Россия

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 бромида 3-(4,5-диметилтиазол-2-ил)-2,5-тетразолия (MTT).

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.

Как цитировать:
Власова Ю.А., Загородникова К.А. Метаболит N-ацетил-парабензохинонимин как фактор возможной нейротоксичности парацетамола // Вестник Северо-Западного государственного медицинского университета им. И.И. Мечникова. 2021. Т. 13. № 4. С. 79–84. DOI: https://doi.org/10.17816/mechnikov99620

Рукопись получена: 02.12.2021 **Рукопись одобрена:** 14.12.2021 **Опубликована:** 29.12.2021

ЭКО•ВЕКТОР

DOI: https://doi.org/10.17816/mechnikov99620

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

Yuliya A. Vlasova, Ksenia A. Zagorodnikova

North-Western State Medical University named after I.I. Mechnikov, Saint Petersburg, Russia

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.

To cite this article:
Vlasova YuA, Zagorodnikova KA. N-acetyl-p-benzoquinonimine metabolite as a factor of possible neurotoxicity of paracetamol. *Herald of North-Western State Medical University named after I.I. Mechnikov.* 2021;13(4):79–84. DOI: https://doi.org/10.17816/mechnikov99620

Received: 02.12.2021 **Accepted:** 14.12.2021 **Published:** 29.12.2021

ECO•VECTOR

DOI: https://doi.org/10.17816/mechnikov99620

N-acetyl-parabenzoquinonimine代谢物是扑热息痛可能产生的神经毒性的一个因素

Yuliya A. Vlasova, Ksenia A. Zagorodnikova

North-Western State Medical University named after I.I. Mechnikov, Saint Petersburg, Russia

论证： 在现代科学文献中，扑热息痛对中枢神经系统可能产生的负面影响被广泛讨论，特别是在怀孕期间摄入它与儿童自闭症谱系障碍的风险之间的联系。关于这个话题有很多问题评估行为障碍和处理研究结果的方法因此，获得神经元细胞上的实验数据可能是足够的证据来证实或反驳关于扑热息痛及其代谢物的神经毒性的假设。

项研究的目的是研究对乙酰氨基酚的作用，及其代谢物Nacetyl-parabenzoquinonimine (NAPQI)对胎鼠大脑皮层神经元的影响。

材料与方法： 通过基于3-(4,5-二甲基噻唑-2-基)-2,5-溴化四唑(MTT)还原的方法研究扑热息痛及其代谢物对细胞活力的影响。

结果： 在用浓度为1毫克/毫升的扑热息痛预孵育大鼠大脑皮层神经元24小时，随后用0.3 mM过氧化氢孵育期间，确定了这些物质对神经元活力降低的影响，包括与它们一起孵化时。当与扑热息痛或其代谢物和过氧化氢共同预孵育时发现了同样的效果。

结论： 扑热息痛及其代谢物NAPQI均可降低大鼠胎儿皮层神经元活力。

关键词： 神经元；RS12线；扑热息痛；纳普齐。

引用本文：
Vlasova YuA, Zagorodnikova KA. N-acetyl-parabenzoquinonimine代谢物是扑热息痛可能产生的神经毒性的一个因素. *Herald of North-Western State Medical University named after I.I. Mechnikov.* 2021;13(4):79–84. DOI: https://doi.org/10.17816/mechnikov99620

收稿日期： 2021年12月2日 **审稿日期：** 2021年12月14日 **出版时间：** 2021年12月29日

论证

对乙酰氨基酚（acetaminophen）是最常见的解热镇痛药，其副作用比大多数非甾体类抗炎药小，其特点是对胃肠道的损害，增加肾脏的全身血管阻力由于前列腺素合成受损导致的损伤和液体潴留。由于其受欢迎程度和被认为具有高度安全性使用怀孕期间。美国使用25-40%的孕妇，其中3-20%在所有三个三个月内[1]。如果超过剂量，对乙酰氨基酚有肝毒性作用,并根据学者的说法，是美国和欧洲最常见的肝功能衰竭原因。44%的健康志愿者中，单剂量的扑热息痛引起肝转氨酶升高[2]。

扑热息痛毒性的核心在于它的代谢（图1），其次要途径导致形成N-acetyl-parabenzoquinonimine（NAPQI）。

定期使用扑热息痛代谢物是无害的。它被谷胱甘肽-S-转移酶快速结合并在胆汁中排泄。极少数情况下，它与蛋白质的巯基共价结合形成稳定的蛋白质加合物，通常会被自噬去除[3]。在服用高剂量对乙酰氨基酚并随后达到饱和极限的情况下进行NAPQI积累。这种情况下，线粒体蛋白被转化为不可逆形成的非功能结合物，发生谷胱甘肽缺乏，发生氧化应激反应，并引发细胞凋亡[4]。扑热息痛的毒性作用的诱发因素是疲惫、长期饮食（谷胱甘肽储备耗尽）、饮酒（诱导CYP2E1系统中的新陈代谢）以及恢复肝细胞的胆汁酸含量降低[5]。

与扑热息痛代谢相关的详细毒性机制，以及这种药物在孕妇中广受欢迎的已知事实，都值得关注。NAPQI的形成取决于妊娠期间活性增加的酶[6]，即CYP2A6、CYP3A4和CYP2D6家族的细胞色素。同时不能排除NAPQI毒性对发育中的胎儿神经系统构成威胁，胎儿神经系统易受外部因素影响。研究表明，母亲在怀孕期间使用扑热息痛之间存在关联和大龄儿童的行为障碍[7]。我们在一项实验中分析了扑热息痛和NAPQI对神经系统细胞的毒性。

本研究的目的是在过氧化氢诱导的氧化应激条件下，研究对乙酰氨基酚代谢产物NAPQI对大鼠大脑皮层神经元的影响。

材料与方法

以下用于研究：过氧化氢、扑热息痛、胞嘧啶-β-D-阿拉伯糖苷呋喃糖苷、Sigma (USA)的聚-D-赖氨酸、含有L-谷氨酰胺的培养培养基DMEM、胎牛血清、胰蛋白酶、青霉素和BioloT（俄罗斯）的链霉素。

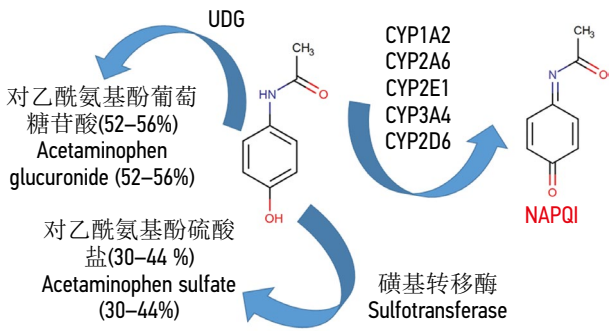

图1 对乙酰氨基酚的代谢。NAPQI，N-乙酰基-对苯醌亚胺；UDG－UDP-葡萄糖醛酸转移酶

Fig. 1. Metabolism of paracetamol. NAPQI — N-acetyl-p-benzoquinonimine; UDG — uridine-diphosphate (UDG)-glucuronosyl transferase

在开发的第17-18天从大鼠胚胎大脑皮层分离的神经元[8]。为细胞分离使用了胰蛋白酶，为防止胶质细胞增殖使用胞嘧啶-β-D-阿拉伯糖苷呋喃糖苷。神经元在完全DMEM生长培养基中生长，含有10% F12培养基、10%胎牛血清、2 mM L-谷氨酰胺和20 mM HEPES。将神经元细胞接种在96孔板中的完全生长培养基中，每孔涂有4×10^5个聚-D-赖氨酸。第二天，用1 μM胞嘧啶-β-D阿拉伯呋喃糖苷处理细胞，24小时后更换为完全培养基。第5-6天开始*in vitro*细胞培养的实验。

测定细胞活力通过基于还原3-(4,5-二甲基噻唑-2-基)-2,5-溴化四唑(MTT)的方法[9]。将细胞以每孔5×10^4的浓度接种到96孔板中。24小时后，将完全生长培养基更换为含有L-谷氨酰胺的DMEM培养基。24小时内它们与浓度为1毫克/毫升的扑热息痛或NAPQI(0.1毫克/毫升)一起孵育。孵化结束前2.5小时加入0.3 mM过氧化氢。孵育结束前2小时加入浓度为0.5毫克/毫升的MTT试剂2个小时后用20%十二烷基硫酸钠在0.05 N HCl溶液中的50%二甲基甲酰胺溶液中裂解细胞。在570纳米有色反应产物（MTT-甲臜）的含量在酶标仪上通过确定光密度来测量。结果表示为对照值的百分比就是未暴露于扑热息痛、NAPQI和过氧化氢的PC12细胞中的条件100%MTT-甲臜。

线粒体膜电位的变化使用阳离子染料JC-1通过流式细胞仪检查。24小时内细胞与浓度为1毫克/毫升的扑热息痛一起孵育或NAPQI(0.1毫克/毫升)孵化结束前一小时加入0.3 mM过氧化氢。孵育结束前0.5小时添加终浓度的染料JC-1。在FL1=525±40 nm、FL2 575±30 nm、λ_{ex}=488 nm的FC-500流式细胞仪(Beckman Coulter)上进行测量。评估和量化从红色到绿色的颜色变化。结果以未暴露于研究物质的PC12细胞对照值的百分比表示。

结果与讨论

在图2显示了第一个典型实验的结果。与0.3 mM过氧化氢、1毫克/毫升对乙酰氨基酚和NAPQI(0.1毫克/毫升)预孵育可将存活细胞的百分比分别降低至51.5%、85.2%和85.6%。与过氧化氢和扑热息痛或NAPQI共同孵育显示神经元活力（高达52.8%）比对照细胞更显着降低。

这种预孵育还将线粒体膜电位分别降低至90.0%、90.7%和90.5%（图3）。与过氧化氢和扑热息痛或NAPQI共同孵育显示，线粒体膜电位比对照细胞分别下降更大，分别为88.9%和80.6%。

扑热息痛对胎儿大脑发育的影响是一个争论的话题。丹麦国家出生登记处的一项分析显示，孕妇使用扑热息痛与出生儿童的自闭症谱系障碍之间存在关联[10]。在对其他队列的分析中也发现了类似的结果：挪威MoBa队列[11]和护士健康研究队列，这是旨在研究女性健康的最大登记处之一[12]。对已发表研究的荟萃分析证实了孕妇服用扑热息痛与儿童注意力缺陷多动障碍风险之间的关系[13]。

识别关联时对乙酰氨基酚及其代谢物浓度的测量是难得，由于研究结果的异质性。该药物的剂量在怀孕期间被认为是安全的，目前尚不清楚[14]。

动物实验的数据不太多。C. Rigobello和合著者发现怀孕大鼠使用扑热息痛后，它们的幼崽在两个月大时表现出社会不适应、认知障碍以及下丘脑、小脑和脊髓中单胺代谢紊乱的迹象[15]。

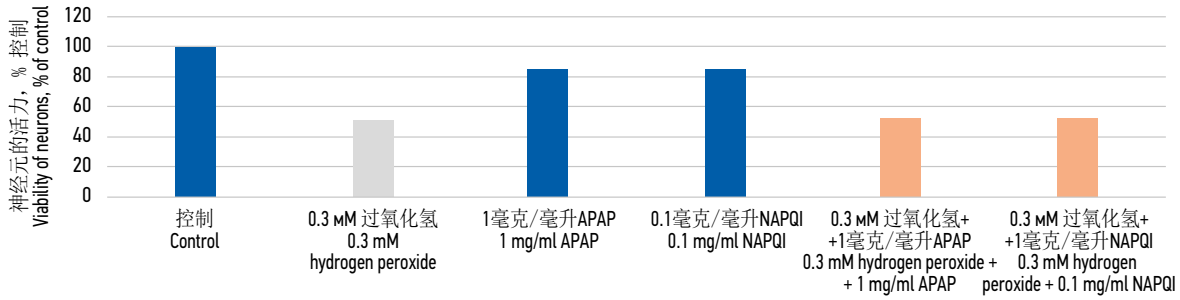

图2 对乙酰氨基酚和N-acetyl-parabenzoquinonimine对胎鼠大脑皮层神经元存活的影响。APAP—扑热息痛；NAPQI—N-acetyl-parabenzoquinonimine

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

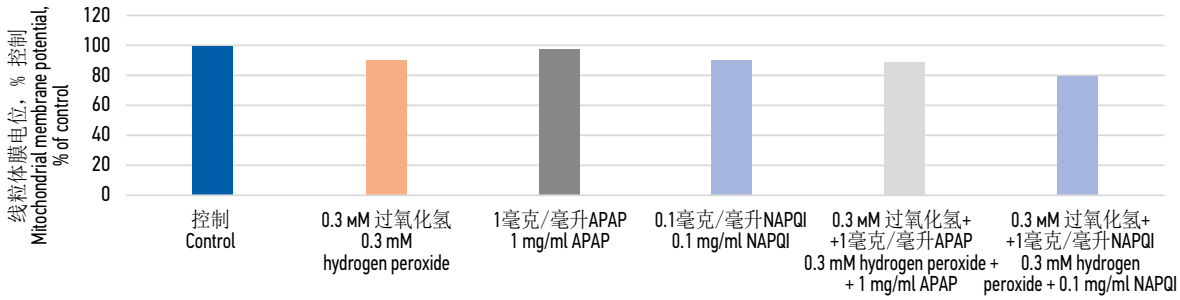

图3 扑热息痛和N--acetyl-parabenzoquinonimine对苯醌亚胺对胎鼠大脑皮层神经元线粒体膜电位变化的影响。APAP—扑热息痛；NAPQI—N-acetyl-parabenzoquinonimine

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

实验表明，扑热息痛可显着增加人胶质母细胞瘤A172球体中细胞凋亡标志物JNK、HIF1A和CASP3的表达[16]。我们已经证明，在1 mM和2 mM浓度下，扑热息痛会增加神经元系PC12的细胞死亡[17, 18]。

还有证据表明在小鼠中对乙酰氨基酚引起认知障碍和大脑不同部位神经营养因子数量的变化（额叶皮质增加和颞叶减少）[19]。

结论

我们之前已经表明，扑热息痛可能对神经元谱系PC12的细胞产生毒性作用[9, 17, 18]。获得对乙酰氨基酚及其代谢物NAPQI降低胎鼠大脑皮层神经元活力和线粒体膜电位的数据，就可以表明这种药物可能对神经组织产生毒性作用。我们的研究有助于描述可能解释扑热息痛的神经毒性作用的生物学机制，特别是对发育中的胎儿大脑的影响。有必要研究与妊娠期CYP2D6和CYP3A4活性变化相关的NAPQI形成特征。我们认为，最困难的任务是确定怀孕期间对乙酰氨基酚使用的临界剂量和期限，这是实施其神经毒性所必需的。

附加信息

资金来源。本研究是在俄罗斯联邦卫生部在科学活动方面的财政支持下进行的（政府分配号：AAAA-A19-119060390106-0）。

利益冲突。作者声明，没有明显的和潜在的利益冲突相关的发表这篇文章。

所有作者都对文章的研究和准备做出了重大贡献，在发表前阅读并批准了最终版本。

REFERENCES

1. Bandoli G, Palmsten K, Chambers C. Acetaminophen use in pregnancy: Examining prevalence, timing, and indication of use in a prospective birth cohort. *Paediatr Perinat Epidemiol.* 2020;34(3):237–246. DOI: 10.1111/ppe.12595

2. Chiew AL, Buckley NA. Acetaminophen Poisoning. *Crit Care Clin.* 2021;37(3):543–561. DOI: 10.1016/j.ccc.2021.03.005

3. Ni HM, McGill MR, Chao X, et al. Removal of acetaminophen protein adducts by autophagy protects against acetaminophen-induced liver injury in mice. *J Hepatol.* 2016;65(2):354–362. DOI: 10.1016/j.jhep.2016.04.025

4. Ramachandran A, Jaeschke H. Acetaminophen toxicity: Novel insights into mechanisms and future perspectives. *Gene Expr.* 2018;18(1):19–30. DOI: 10.3727/105221617X15084371374138

5. Tujios S, Fontana RJ. Mechanisms of drug-induced liver injury: from bedside to bench. *Nat Rev Gastroenterol Hepatol.* 2011;8(4):202–211. DOI: 10.1038/nrgastro.2011.22

6. Eke AC. An update on the physiologic changes during pregnancy and their impact on drug pharmacokinetics and pharmacogenomics. *J Basic Clin Physiol Pharmacol.* 2021. DOI: 10.1515/jbcpp-2021-0312

7. Stergiakouli E, Thapar A, Davey Smith G. Association of acetaminophen use during pregnancy with behavioral problems in childhood: evidence against confounding. *JAMA Pediatr.* 2016;170(10):964–970. DOI: 10.1001/jamapediatrics.2016.1775

8. Avrova NF, Sokolova TV, Vlasova YA, et al. Protective and antioxidative effects of GM1 ganglioside in PC12 cells exposed to hydrogen peroxide are mediated by trk tyrosine kinase. *Neurochem Res.* 2010;35(1):85–98. DOI: 10.1007/s11064-009-0033-6

9. Vlasova YuA, Golovanova NE, Beishebaeva ChR, et al. Study of neurotoxicity of paracetamol and its metabolite NAPQI (short message). *Laboratory Animals for Science.* 2021;4. DOI: 10.29296/2618723X-2021-04-09

10. Liew Z, Ritz B, Virk J, Olsen J. Maternal use of acetaminophen during pregnancy and risk of autism spectrum disorders in childhood:

A Danish national birth cohort study. *Autism Res.* 2016;9(9):951–958. DOI: 10.1002/aur.1591
11. Ystrom E, Gustavson K, Brandlistuen RE, et al. Prenatal Exposure to Acetaminophen and Risk of ADHD. *Pediatrics*. 2017;140(5):e20163840. DOI: 10.1542/peds.2016-3840
12. Liew Z, Kioumourtzoglou MA, Roberts AL, et al. Use of negative control exposure analysis to evaluate confounding: an example of acetaminophen exposure and attention-deficit/hyperactivity disorder in Nurses' Health Study II. *Am J Epidemiol*. 2019;188(4):768–775. DOI: 10.1093/aje/kwy288
13. Gou X, Wang Y, Tang Y, et al. Association of maternal prenatal acetaminophen use with the risk of attention deficit/hyperactivity disorder in offspring: A meta-analysis. *Aust NZ J Psychiatry.* 2019;53(3):195–206. DOI: 10.1177/0004867418823276
14. Bührer C, Endesfelder S, Scheuer T, Schmitz T. Paracetamol (Acetaminophen) and the developing brain. *Int J Mol Sci.* 2021;22(20):11156. DOI: 10.3390/ijms222011156
15. Rigobello C, Klein RM, Debiasi JD, et al. Perinatal exposure to paracetamol: Dose and sex-dependent effects in behaviour and brain's oxidative stress markers in progeny. *Behav Brain Res.* 2021;408:113294. DOI: 10.1016/j.bbr.2021.113294
16. Aleksandrova AV, Senyavina NV, Maltseva DV, et al. p53- and Caspase-3-independent mechanism of acetaminophen effect on human neural cells. *Bull Exp Biol Med*. 2016;160(6):763–766. DOI: 10.1007/s10517-016-3304-7
17. Vlasova YuA, Zagorodnikova KA, Ivanova IS, Chukhno AS. The impact of oxidative stress on the neurotoxic effect of acetaminophen. *Butlerov Communications.* 2019;59(9):106–109. (In Russ.)
18. Vlasova YuA, Zagorodnikova KA, Gajkovaya LB. Acetaminofen (paracetamol) v vysokikh koncentraciyakh snizhaet zhiznesposobnost' kletok RS12. Proceedings of the Vserossijskaya nauchno-prakticheskaya konferenciya s mezhdunarodnym uchastiem "Profilakticheskaya medicina – 2019"; Sankt-Peterburg, Nov 14–15, 2019. Saint Petersburg; 2019. P. 110–115. (In Russ.)
19. Schultz S, DeSilva M, Gu T, et al. Effects of the analgesic acetaminophen (paracetamol) and its para-aminophenol metabolite on viability of mouse-cultured cortical neurons. *Basic Clin Pharmacol Toxicol.* 2012;110(2):141–144. DOI: 10.1111/j.1742-7843.2011.00767.x

СПИСОК ЛИТЕРАТУРЫ

1. Bandoli G., Palmsten K., Chambers C. Acetaminophen use in pregnancy: Examining prevalence, timing, and indication of use in a prospective birth cohort // Paediatr. Perinat. Epidemiol. 2020. Vol. 34, No. 3. P. 237–246. DOI: 10.1111/ppe.12595
2. Chiew A.L., Buckley N.A. Acetaminophen Poisoning // Crit. Care Clin. 2021. Vol. 37, No. 3. P. 543–561. DOI: 10.1016/j.ccc.2021.03.005
3. Ni H.M., McGill M.R., Chao X. et al. Removal of acetaminophen protein adducts by autophagy protects against acetaminophen-induced liver injury in mice // J. Hepatol. 2016. Vol. 65, No. 2. P. 354–362. DOI: 10.1016/j.jhep.2016.04.025
4. Ramachandran A., Jaeschke H. Acetaminophen toxicity: Novel insights into mechanisms and future perspectives // Gene Expr. 2018. Vol. 18, No. 1. P. 19–30. DOI: 10.3727/105221617X15084371374138
5. Tujios S., Fontana R.J. Mechanisms of drug-induced liver injury: from bedside to bench // Nat. Rev. Gastroenterol. Hepatol. 2011. Vol. 8, No. 4. P. 202–211. DOI: 10.1038/nrgastro.2011.22
6. Eke A.C. An update on the physiologic changes during pregnancy and their impact on drug pharmacokinetics and pharmacogenomics // J. Basic Clin. Physiol. Pharmacol. 2021. DOI: 10.1515/jbcpp-2021-0312
7. Stergiakouli E., Thapar A., Davey Smith G. Association of acetaminophen use during pregnancy with behavioral problems in childhood: evidence against confounding // JAMA Pediatr. 2016. Vol. 170, No. 10. P. 964–970. DOI: 10.1001/jamapediatrics.2016.1775
8. Avrova N.F., Sokolova T.V., Vlasova Y.A. et al. Protective and antioxidative effects of GM1 ganglioside in PC12 cells exposed to hydrogen peroxide are mediated by trk tyrosine kinase // Neurochem. Res. 2010. Vol. 35, No. 1. P. 85–98. DOI: 10.1007/s11064-009-0033-6
9. Власова Ю.А., Голованова Н.Э., Бейшебаева Ч.Р. и др. Исследование нейротоксичности парацетамола и его метаболита NAPQI (краткое сообщение) // Лабораторные животные для научных исследований. 2021. Т. 4. DOI: 10.29296/2618723X-2021-04-09
10. Liew Z., Ritz B., Virk J., Olsen J. Maternal use of acetaminophen during pregnancy and risk of autism spectrum disorders in childhood: A Danish national birth cohort study // Autism. Res. 2016. Vol. 9, No. 9. P. 951–958. DOI: 10.1002/aur.1591
11. Ystrom E., Gustavson K., Brandlistuen R.E. et al. Prenatal Exposure to Acetaminophen and Risk of ADHD // Pediatrics. 2017. Vol. 140, No. 5. P. e20163840. DOI: 10.1542/peds.2016-3840
12. Liew Z., Kioumourtzoglou M.A., Roberts A.L. et al. Use of negative control exposure analysis to evaluate confounding: an example of acetaminophen exposure and attention-deficit/hyperactivity disorder in Nurses' Health Study II // Am. J. Epidemiol. 2019. Vol. 188, No. 4. P. 768–775. DOI: 10.1093/aje/kwy288
13. Gou X., Wang Y., Tang Y. et al. Association of maternal prenatal acetaminophen use with the risk of attention deficit/hyperactivity disorder in offspring: A meta-analysis // Aust. N.Z. J. Psychiatry. 2019. Vol. 53, No. 3. P. 195–206. DOI: 10.1177/0004867418823276
14. Bührer C., Endesfelder S., Scheuer T., Schmitz T. Paracetamol (Acetaminophen) and the Developing Brain // Int. J. Mol. Sci. 2021. Vol. 22, No. 20. P. 11156. DOI: 10.3390/ijms222011156
15. Rigobello C., Klein R.M., Debiasi J.D. et al. Perinatal exposure to paracetamol: Dose and sex-dependent effects in behaviour and brain's oxidative stress markers in progeny // Behav. Brain Res. 2021. Vol. 408. P. 113294. DOI: 10.1016/j.bbr.2021.113294
16. Aleksandrova A.V., Senyavina N.V., Maltseva D.V. et al. p53- and Caspase-3-independent mechanism of acetaminophen effect on human neural cells // Bull. Exp. Biol. Med. 2016. Vol. 160, No. 6. P. 763–766. DOI: 10.1007/s10517-016-3304-7
17. Власова Ю.А., Загородникова К.А., Иванова И.С., Чухно А.С. Влияние окислительного стресса на нейротоксический эффект ацетаминофена // Бутлеровские сообщения. 2019. Т. 59, № 9. С. 106–109.
18. Власова Ю.А., Загородникова К.А., Гайковая Л.Б. Ацетаминофен (парацетамол) в высоких концентрациях снижает жизнеспособность клеток PC12 // Профилактическая медицина – 2019: сборник научных трудов Всероссийской научно-практической конференции с международным участием, Санкт-Петербург, 14–15 ноября 2019 года. СПб., 2019. С. 110–115.
19. Schultz S., DeSilva M., Gu T. et al. Effects of the analgesic acetaminophen (paracetamol) and its para-aminophenol metabolite on viability of mouse-cultured cortical neurons // Basic Clin. Pharmacol.Toxicol. 2012. Vol. 110, No. 2. P. 141–144. DOI: 10.1111/j.1742-7843.2011.00767.x

AUTHORS INFO

*** Yuliya A. Vlasova**, PhD, Cand. Sci. (Biol.), Assistant Professor; address: 47 Piskarevsky Ave., Saint Petersburg, 195067, Russia; ORCID: https://orcid.org/0000-0001-5536-3595; Scopus Author ID: 6701810182; e-mail: Yuliya.Vlasova@szgmu.ru

Ksenia A. Zagorodnikova, MD, Cand. Sci. (Med.), Assistant Professor; e-mail: ksenia.zagorodnikova@gmail.com

ОБ АВТОРАХ

*** Юлия Александровна Власова**, канд. биол. наук, доцент; адрес: Россия, 195067, Санкт-Петербург, Пискаревский пр., д. 47; ORCID: https://orcid.org/0000-0001-5536-3595; Scopus Author ID: 6701810182; e-mail: Yuliya.Vlasova@szgmu.ru

Ксения Александровна Загородникова, канд. мед. наук, доцент; e-mail: ksenia.zagorodnikova@gmail.com

* Corresponding author / Автор, ответственный за переписку