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CHANGES IN THE AMOUNTS OF SOME NEUROTRANSMITTERS IN THE BRAIN OF RATS EXPOSED TO MORPHINE DURING THE PRENATAL PERIOD

Research article

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Abstract

The impact of exposure to morphine on the balance of neurotransmitters in developing brain tissue during prenatal period has been one of the focal issues in recent years. In present study, the impact of morphine on the amount of GABA and the main excitatory amino acids (glutamate and aspartate) during organogenesis, which is one of the critical stages of prenatal ontogenesis, was examined. The results showed that after exposure to low doses of morphine (2 mg/kg, twice a day) in maternal rats, the amount of GABA in the brain structures of the offspring increased, and the levels of glutamate and aspartate decreased. However, after exposure to high doses of morphine (10 mg/kg, twice a day) in prenatal ontogenesis, the amount of GABA in the brain structures of rats decreased. The amount of other studied neurotransmitters — glutamate and aspartate - increased.

The results show that in prenatal ontogenesis, low-dose morphine leads to a metabolic strengthening of the inhibitory system and a weakening of the excitatory system. These changes may lead to a shift of the excitation–inhibition balance toward inhibition in the developing brain. The increase in GABA levels may represent a compensatory adaptation of the system.

The administration of high doses of morphine to maternal rats causes irreversible disturbances in GABA metabolism in the brain of their offspring, indicating that the excitatory system prevails over the inhibitory system. The excitatory glutamate and glutamate receptors play an important role in both physiological and pathological reactions in the CNS. An excessive increase in the amount of glutamate in the brain results in a shift from its physiological function to a pathological one. This leads to the death of neurons, the development of inflammatory processes in the brain, and long-term stress.

Keywords: morphine, prenatal period, gamma-aminobutyric acid, glutamate, aspartate.

ИЗМЕНЕНИЕ СОДЕРЖАНИЯ НЕКОТОРЫХ НЕЙРОТРАНСМИТТЕРОВ В ГОЛОВНОМ МОЗГЕ КРЫС, ПОДВЕРГШИХСЯ ВОЗДЕЙСТВИЮ МОРФИНА В ПРЕНАТАЛЬНЫЙ ПЕРИОД

Научная статья

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Аннотация

В последние годы изучение воздействия морфина в пренатальный период на баланс нейромедиаторов в развивающейся ткани мозга находится в центре внимания исследователей. В данной работе изучено влияние морфина в период органогенеза — одного из критических этапов пренатального развития — на содержание ГАМК и основных возбуждающих аминокислот (глутамата и аспартата). Результаты показали повышение содержания ГАМК и снижение уровня глутамата и аспартата в структурах головного мозга у потомства самок крыс, подвергнутых воздействию морфина в низкой дозе (2 мг/кг, 2 раза в сутки). Однако введение высокой дозы морфина (10 мг/кг, 2 раза в сутки) в пренатальном онтогенезе привело к снижению уровня ГАМК в структурах головного мозга крыс, в то время как содержание других исследуемых нейромедиаторов — глутамата и аспартата — повышалось.

Полученные результаты свидетельствуют о том, что воздействие низкой дозы морфина в пренатальном онтогенезе способствует метаболическому усилению тормозной и ослаблению возбуждающей системы, что может приводить к смещению баланса возбуждение–торможение в сторону торможения в развивающемся мозге. Повышение содержания ГАМК может проявляться компенсаторной адаптацией системы.

Введение самкам крыс высокой дозы морфина приводит к необратимым изменениям в метаболизме ГАМК в головном мозге их потомства, что, возможно, указывает на преобладание возбуждающей системы над тормозной. Возбуждающий нейромедиатор глутамат и его рецепторы играют важную роль как в физиологических, так и патологических реакциях ЦНС. Чрезмерная концентрация глутамата в головном мозге приводит к патологическим процессам, включая гибель нейронов, нейровоспаление и формирование хронического стресса.

Ключевые слова: морфин, пренатальный период, гамма-аминомасляная кислота, глутамат, аспартат.

Introduction

Neonatal abstinence syndrome (NAS) occurs as a result of the maternal rat's exposure to various addictive substances during pregnancy. The developing fetus develops an addiction to these substances. One of such substances is morphine.

One of the biggest problems facing the healthcare system in our time is the use of opioids during pregnancy. Opioid analgesics, including morphine, easily cross the placenta, despite its barrier function, and can directly affect the central nervous

system (CNS) of the developing fetus [12]. As is known, during prenatal development, a number of processes begin in the fetal central nervous system, including neuronal migration, synaptic formation, and the establishment of the excitation–inhibition balance. Substances that cause NAS, including morphine and other opioids, disrupt these processes, as well as cause long-term functional changes. As a result, serious disturbances in behavior, synaptic plasticity, and cognitive functions can be observed in the postnatal period [6].

The GABA and glutamate systems and their receptors are of particular importance during both prenatal and postnatal development [7], [11]. In prenatal ontogenesis, GABA acts as an excitatory mediator, and glutamate acts as an inhibitory mediator, and these mediators change their functions with synaptic maturation, that is, GABA plays the role of an inhibitory mediator, and glutamate plays the role of an excitatory mediator [17]. The timely occurrence of this transition is of vital importance for normal cortical development and the functioning of neuronal networks.

Prenatal morphine exposure can alter the synthesis of GABA and glutamate, the expression of receptor subunits, and inhibitory synaptic transmission. Early embryonic exposure to morphine significantly delays the formation of GABAergic synapses [18]. The study found out that morphine reduces the density and functional activity of GABA synapses in avian embryos, as well as the activity of the GAD enzyme. The GAD enzyme is a key regulator of GABA synthesis, so its reduction results in a weakening of the overall inhibitory process.

However, the mechanism of changes in the level of excitatory and inhibitory mediators depending on the dose of morphine during prenatal ontogenesis has not yet been fully elucidated. In this regard, the study of all components involved in GABA metabolism under appropriate conditions is of great scientific importance.

Research methods and principles

50 female white rats, aged 6 months, were divided into 2 groups. Group I — control animals, group II — morphine-injected animals. Control animals were injected with saline solution into the abdominal cavity. Group II animals were divided into 2 subgroups: animals injected with morphine intraperitoneally at doses of 2 mg/kg and 10 mg/kg. Saline solution and morphine were injected intraperitoneally into the animals during the organogenesis period (on the 8th–14th day of gestation) twice a day (at 10:00 and 6:00). 1-month-old offspring of all groups were decapitated, and their brains were divided into structures. In our experiments, the amount of neurotransmitters GABA, Glu and Asp was determined in the cortex, cerebellum, brain stem and hypothalamus of the cerebral hemispheres [1].

All experimental studies were approved by the Local Ethics Committee of the Azerbaijan Pedagogical University (Protocol No. 02/2023, approved on May 6, 2023) and were carried out in accordance with international standards for animal welfare (EU Directive 2010/63/EU).

The results were statistically processed using Student's t-test and Statistics for Windows and Microsoft Excel programs.

Main results

In the experiments, the amount of GABA, Glu and Asp was initially determined in the studied structures of the brain in control animals. In subsequent experiments, the amount of the studied neurotransmitters — GABA, glutamate and aspartate — was studied in the brain structures of animals exposed to morphine in prenatal ontogenesis and compared with control indicators.

In prenatal ontogenesis, after exposure to low doses of morphine, the amount of GABA in the cerebral cortex, cerebellum, brainstem, and hypothalamus of 1-month-old rats is 31%, 35%, 28%, and 24% higher, respectively, compared to control animals. The amount of glutamate is 25%, 28%, 22%, and 29% lower, respectively. The decrease in the amount of aspartate is 20%, 24%, 18%, and 17%, respectively (table). In prenatal ontogenesis, after exposure to high doses of morphine, the amount of GABA in the cerebral cortex, cerebellum, brainstem, and hypothalamus of 1-month-old rats is 35%, 41%, 33%, and 30% lower, respectively, compared to intact animals. The amount of glutamate is 50%, 67%, 48%, and 35% higher, respectively. The increase in the amount of aspartate was 49%, 53%, 45% and 38%, respectively (table).

Table 1 - Changes in the amount of GABA, Glu and Asp (μmol/g) in various structures of the brain of rats exposed to morphine during organogenesis (M±m, n=5)

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Brain structures	Condition of the experiment	Indicators	1 month		
			GABA	Glu	Asp
Cerebral cortex of the brain hemispheres	Control	M±m	2.72±0.06	4.70±0.14	3.29±0.08
	2 mg/kg, twice a day	M±m	3.56±0.11***	3.53±0.12**	2.63±0.10**
		%	131	75	80
	10 mg/kg, twice a day	M±m	1.77±0.05***	7.05±0.22***	4.90±0.14***
		%	65	150	149
Cerebellum	Control	M±m	2.40±0.07	5.07±0.16	3.10±0.07
	2 mg/kg, twice a day	M±m	3.24±0.15**	3.65±0.14***	2.36±0.09***
		%	135	72	76
	10 mg/kg, twice a day	M±m	1.42±0.07***	8.47±0.26***	4.74±0.11***
		%	59	167	153
Brainstem	Control	M±m	2.08±0.04	5.24±0.13	2.87±0.05

Brain structures	Condition of the experiment	Indicators	1 month		
			GABA	Glu	Asp
	2 mg/kg, twice a day	M±m	2.66±0.07***	4.09±0.13***	2.35±0.07***
		%	128	78	82
	10 mg/kg, twice a day	M±m	1.39±0.05***	7.76±0.28***	4.16±0.14***
		%	67	148	145
Hypothalamus	Control	M±m	3.20±0.11	5.87±0.19	3.64±0.07
	2 mg/kg, twice a day	M±m	3.97 ±0.14**	4.70±0.16**	3.02±0.08***
		%	124	80	83
	10 mg/kg, twice a day	M±m	2.24±0.10***	7.92±0.28***	5.02±0.15***
		%	70	135	138

*Note: * – $p<0.05$, ** – $p<0.01$, *** – $p<0.001$*

The analysis of the results obtained shows that the dynamics of changes in the studied neurotransmitters in different experimental conditions demonstrate a direct dependence on the dose of morphine applied in prenatal ontogenesis. A comparative analysis of the indicators of the conducted study shows that both the comparison of the results between groups and the parallel evaluation of these results with the data contained in the existing scientific literature reveal the presence of certain similar and different trends. The observed similarities and contradictions confirm that the mechanisms of prenatal action of morphine are multicomponent and multifactorial in nature, and can also vary under the influence of different experimental conditions, doses and biological characteristics.

The results of our study showed that the effect of morphine in different doses in prenatal ontogenesis causes changes in the levels of GABA, glutamate and aspartate in the brain structures. We would like to specifically note that against the background of an increase in the amount of GABA, a decrease in the amount of glutamate and aspartate occurred. In another case, when the amount of GABA decreased, the amount of glutamate and aspartate increased. These results indicate that in both cases, the imbalance between excitatory and inhibitory processes occurred as a result of a change in the activity of both processes. However, the direction of the changes that occurred depended on the dose of morphine in prenatal ontogenesis.

Let us compare and discuss our results with literature references: The increase in the amount of GABA after exposure to low doses of morphine in prenatal ontogenesis indicates that morphine can cause an increase in inhibitory processes in the developing nervous system. The increase in GABA seems to contradict existing studies on the weakening of GABA synapses by morphine [18]. However, the increase in the amount of GABA as a result of the influence of many harmful factors in prenatal ontogenesis is explained by compensatory mechanisms [2], [4]. This change found out in our studies also occurs on the basis of metabolic and compensatory mechanisms. When these adaptations are accompanied by a weakening of the receptor level or synaptic structural disorders, the body may try to eliminate the functional deficiency by metabolically increasing the production of GABA.

In our studies, the decrease in the levels of both glutamate and aspartate after exposure to low doses of morphine in prenatal ontogenesis indicates that morphine affects the excitatory amino acid system. The decrease in glutamate can be explained by two main mechanisms: the increased GAD activity leads to a greater redirection of glutamate to GABA synthesis [11] and the mechanism of prenatal morphine weakening of glutamatergic synaptogenesis, as shown by Simmons et al. [16]. The decrease in aspartate indicates that morphine can cause disorders in a wide range of amino acid metabolism.

Ramshini E. et al. have shown that morphine administration not only increases the level of GABA, but also reduces the level of Glu in the medial prefrontal cortex (mPFC) [15]. Activation of opioid receptors by morphine enhances the activity of GABAergic neurons in the PFC, which may have an inhibitory effect on the activity of Glu-ergic pyramidal neurons [14]. Morphine exposure inhibits GABAergic interneurons in the ventral tegmental area (VTA) and results in increased dopamine release into the PFC. This process may directly or indirectly lead to the inhibition of Gluergic neurons in the PFC by activating GABAergic neurons [15].

The results indicate that prenatal morphine exposure induces metabolic enhancement in the inhibitory system, while substrate deficiency and synaptic weakening are observed in the excitatory system. This may lead to a change in the excitatory–inhibitory balance in the developing brain towards inhibition. Disruption of excitatory-inhibitory balance can result in various neurofunctional changes in the postnatal period — impairment of synaptic plasticity, behavioral disorders, and cognitive difficulties [6].

As shown above, the effects of high doses of morphine in prenatal ontogenesis have led to different results in the neurotransmitters studied in brain structures in postnatal ontogenesis compared to low doses. The results of the study showed that prenatal exposure to morphine causes multifaceted and profound biochemical changes in the GABA system. The decrease in GABA levels, as well as the increase in the levels of key excitatory amino acids such as glutamate and aspartate, indicate that morphine has complex mechanisms of action on developing neuronal networks. Although these results are new, they are consistent with the existing international literature and can be explained by a number of mechanisms.

Decrease in GABA levels as a result of prenatal morphine exposure. The decrease in GABA levels coincides with the negative effect of morphine on inhibitory synaptogenesis in the prenatal period. As shown by Wang et al. [18], early embryonic exposure to morphine reduces the density of GABA synaptic markers and changes the structural composition of GABA_A receptors. These synaptic impairments may naturally be paralleled by the weakening of GABA synthesis. The decrease in GABA levels may also be due to morphine increasing presynaptic inhibition in GABAergic neurons via opioid receptors.

Nervous tissue is highly sensitive to glutamate concentrations. Studies have shown that even a prolonged increase in glutamate levels outside the brain of even 10% (considered glutamate neurotoxicity) can lead to the onset of neurodegenerative processes in the brain [8]. Excessive increase in glutamate levels in the brain results in its transition from a physiological function to a pathological function. This leads to neuronal death, inflammatory processes in the brain, and long-term stress [10]. Maternal use of morphine may cause irreversible disturbances in GABA metabolism in the brain of their offspring.

Glutamate receptors (NMDA, AMPA, and metabotropic subtypes) are considered to be key regulators of neuroadaptive mechanisms involved in the development and maintenance of morphine tolerance. These receptor systems are directly involved in the strengthening and reorganization of synaptic transmission, as well as the formation of long-term changes in the activity of neuronal networks. Activation of excitatory glutamate receptors is closely linked to the activation of a number of critical processes that promote morphine tolerance, including changes in synaptic plasticity, neuroinflammatory responses associated with microglial and astrocytic activation, and multiple downstream signaling pathways, such as MAPK, PKC, and Ca^{2+}-dependent signaling cascades [3]. As a result of these complex interactions, synaptic strength is reorganized and neuronal reactivity is altered during chronic morphine use. As a result, tolerance develops clinically [9].

There is a link between glutamate neurotoxicity and neurodegeneration [13]. Glutamate exsensitivity, that is, excessive accumulation, causes glutamate excitotoxicity. This results in excessive calcium entry into the cell, increases oxidative stress, disrupts mitochondrial function, damages the structure of neurons, and prolonged exposure can result in neurodegeneration [5].

Summing up the results obtained, it can be concluded that the occurrence of fundamental disturbances in the development of the excitatory and inhibitory systems as a result of the influence of morphine in prenatal ontogenesis is significantly dependent on the dose of morphine. The imbalance between inhibitory and excitatory processes caused by the effects of low doses of morphine can be partially reduced by compensatory mechanisms, but the effects of high doses of morphine can cause irreversible disturbances in the metabolism of neurotransmitters and last for many years.

Discussion

In the experiments, the amount of GABA, Glu and Asp was initially determined in the studied structures of the brain in control animals. In subsequent experiments, the amount of the studied neurotransmitters — GABA, glutamate and aspartate — was studied in the brain structures of animals exposed to morphine in prenatal ontogenesis and compared with control indicators.

In prenatal ontogenesis, after exposure to low doses of morphine, the amount of GABA in the cerebral cortex, cerebellum, brainstem, and hypothalamus of 1-month-old rats is 31%, 35%, 28%, and 24% higher, respectively, compared to control animals. The amount of glutamate is 25%, 28%, 22%, and 29% lower, respectively. The decrease in the amount of aspartate is 20%, 24%, 18%, and 17%, respectively (table). In prenatal ontogenesis, after exposure to high doses of morphine, the amount of GABA in the cerebral cortex, cerebellum, brainstem, and hypothalamus of 1-month-old rats is 35%, 41%, 33%, and 30% lower, respectively, compared to intact animals. The amount of glutamate is 50%, 67%, 48%, and 35% higher, respectively. The increase in the amount of aspartate was 49%, 53%, 45% and 38%, respectively (table).

Table 2 - Changes in the amount of GABA, Glu and Asp (μmol/g) in various structures of the brain of rats exposed to morphine during organogenesis (M±m, n=5)

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Brain structures	Condition of the experiment	Indicators	1 month		
			GABA	Glu	Asp
Cerebral cortex of the brain hemispheres	Control	M±m	2.72±0.06	4.70±0.14	3.29±0.08
	2 mg/kg, twice a day	M±m	3.56±0.11***	3.53±0.12**	2.63±0.10**
		%	131	75	80
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Conclusion

As a result of the impact of morphine in prenatal ontogenesis, fundamental changes occur in the amount of neurotransmitters in the brain. These changes depend on the dose of morphine and are of different directions. At low doses, the increase in the amount of GABA in postnatal ontogenesis as a result of the effect of morphine in prenatal ontogenesis occurs due to compensatory mechanisms. At high doses, the decrease in the amount of GABA, the increase in the amount of glutamate and aspartate indicate that the processes of excitation prevail over inhibition and are an indicator of the neurotoxicity of glutamate. Since GABA plays a critical role in the development and functional activity of the nervous system, the clinical consequences of the changes in GABA metabolism caused by prenatal morphine in the developing brain can also be very serious. Therefore, the neurobiological risks associated with the use of opioids during pregnancy should be studied in more depth and neonatal intervention strategies should be expanded.

Конфликт интересов

Не указан.

Рецензия

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Conflict of Interest

None declared.

Review

All articles are peer-reviewed. But the reviewer or the author of the article chose not to publish a review of this article in the public domain. The review can be provided to the competent authorities upon request.

Список литературы / References

1. Алиева Н.Н. Влияние тималина на обмен ГАМК в ткани головного мозга 10-дневных крыс при циклофосфамидной иммуносупрессии / Н.Н. Алиева // Электронный научно-образовательный вестник «Здоровье и образование в XXI веке». — 2016. — Т. 18, № 11. — С. 1–4.

2. Мамедова И.А. Влияние внутриутробной хронической интоксикации этанолом на метаболизм ГАМК в тканях различных структур центральной нервной системы трехмесячных кроликов / И.А. Мамедова // Международный научно-исследовательский журнал. — 2016. — № 10(52). — С. 24–28.

3. Alaee E. Enhancement of neuronal excitability in the medial prefrontal cortex following prenatal morphine exposure / E. Alaee, N. Pachenari, F. Khani, S. Semnanian [et al.] // Brain Research Bulletin. — 2023. — Vol. 204. — P. 110803.

4. Aliyeva N.N. The activity of GABA-T enzyme in the brain of rats in postnatal ontogenesis exposed to hypoxia during fetal period / N.N. Aliyeva // Azerbaijan Journal of Physiology. — 2022. — Vol. 37, № 1. — P. 22–29. — DOI: 10.59883/ajp.4.

5. Al-Nasser M.N. Is L-Glutamate Toxic to Neurons and Thereby Contributes to Neuronal Loss and Neurodegeneration? A Systematic Review / M.N. Al-Nasser, I.R. Mellor, W.G. Carter // Brain Sciences. — 2022. — Vol. 12. — P. 577.

6. Dunn A.D. Molecular and long-term behavioral consequences of neonatal opioid exposure and withdrawal in mice / A.D. Dunn, S.A. Robinson, C. Nwokafor, M. Estill [et al.] // Frontiers in Behavioral Neuroscience. — 2023. — Vol. 17. — P. 1202099. — DOI: 10.3389/fnbeh.2023.1202099.

7. Egbenya D.L. Glutamate receptors in brain development / D.L. Egbenya, E. Aidoo, G. Kyei // Child's Nervous System. — 2021. — Vol. 37. — P. 2753–2758. — DOI: 10.1007/s00381-021-05266-w.

8. Gruenbaum B.F. Glutamate Neurotoxicity and Destruction of the Blood–Brain Barrier: Key Pathways for the Development of Neuropsychiatric Consequences of TBI and Their Potential Treatment Strategies / B.F. Gruenbaum, A. Zlotnik, I. Fleidervish, A. Frenkel [et al.] // International Journal of Molecular Sciences. — 2022. — Vol. 23. — P. 9628. — DOI: 10.3390/ijms23179628.

9. Huang M. Targeting Excitatory Glutamate Receptors for Morphine Tolerance: A Narrative Review / M. Huang, L. Luo, W. Wang, H. Xu [et al.] // CNS Neuroscience & Therapeutics. — 2025. — Vol. 31. — P. e70468. — DOI: 10.1111/cns.70468.

10. Jasper A.H. Glutamatergic Systems and Memory Mechanisms Underlying Opioid Addiction / A.H. Jasper, J. De Vries Taco, P. Jamie // Cold Spring Harbor Perspectives in Medicine. — 2021. — Vol. 11. — P. a039602.

11. Lenin D.O.-de la P. The role of GABA neurotransmitter in the human central nervous system, physiology, and pathophysiology / D.O.-de la P. Lenin, G.-C. Rosario, D´A.-L. Estela [et al.] // Revista Mexicana de Neurociencia. — 2021. — Vol. 22, № 2. — P. 67–76.

12. McAllister J.M. Effects of Prenatal Opioid Exposure on the Brain and Neurodevelopment / J.M. McAllister, S.L. Merhar // Pediatric Clinics of North America. — 2025. — Vol. 72, № 5. — P. 805–823. — DOI: 10.1016/j.pcl.2025.05.012.

13. McGrath T. Emerging Evidence for the Widespread Role of Glutamatergic Dysfunction in Neuropsychiatric Diseases / T. McGrath, R. Baskerville, M. Rogero // Nutrients. — 2022. — Vol. 14. — P. 917.

14. Radhakrishnan R. Neuroimaging in infants with prenatal opioid exposure: current evidence, recent developments and targets for future research / R. Radhakrishnan, G. Grecco, K. Stolze [et al.] // Journal of Neuroradiology. — 2021. — Vol. 48, № 2. — P. 112–120. — DOI: 10.1016/j.neurad.2020.09.009.

15. Ramshini E. Effect of intracerebroventricular injection of GABA receptors antagonists on morphine-induced changes in GABA and Glu transmission within the mPFC: an in vivo microdialysis study / E. Ramshini, H. Alaei, P. Reisi [et al.] // Iranian Journal of Basic Medical Sciences. — 2019. — Vol. 22, № 3. — P. 246–250. — DOI: 10.22038/ijbms.2019.28478.6925.

16. Simmons S.C. Effects of prenatal opioid exposure on synaptic adaptations and behaviors across development / S.C. Simmons, G.G. Grecco, B.K. Atwood // Neuropharmacology. — 2023. — Vol. 222. — P. 109312. — DOI: 10.1016/j.neuropharm.2022.109312.

17. Valeeva G. Excitatory Effects of GABA during Ontogeny / G. Valeeva, R. Khazipov, E.E. Nikolsky // Neuroscience and Behavioral Physiology. — 2013. — Vol. 43, № 5. — P. 656–660. — DOI: 10.1007/s11055-013-9787-z.

18. Wang D. Effect of early embryonic exposure to morphine on defects in the GABAergic system of day-old chicks / D. Wang, J. Jiang, W. Shang [et al.] // Progress in Neuro-Psychopharmacology and Biological Psychiatry. — 2023. — Vol. 121. — P. 110657. — DOI: 10.1016/j.pnpbp.2022.110657.

Список литературы на английском языке / References in English

1. Aliyeva N.N. Vliyanie timalina na obmen GAMK v tkani golovnogo mozga 10-dnevnykh krys pri tsiklofosfamidnoy immunosupressii [The effect of thymalinum on the metabolism GABA in tissues of the brain of 10-day old rats in cyclophosphamide immunosuppression] / N.N. Aliyeva // Elektronnyy nauchno-obrazovatel'nyy vestnik «Zdorov'ye i obrazovaniye v XXI veke» [Online Scientific and Educational Bulletin "Health and Education in the XXI Century"]. — 2016. — Vol. 18, № 11. — P. 1–4. [in Russian]

2. Mamedova I.A. Vliyanie vnutriutrobnoy khronicheskoy intoksikatsii etanolom na metabolizm GAMK v tkanyakh razlichnykh struktur tsentral'noy nervnoy sistemy trekhmesyachnykh krolikov [Influence of intrauterine chronic ethanol intoxication on the GABA metabolism in the tissue of different central nervous system structures of the three month old rabbits] / I.A. Mamedova // Mezhdunarodnyy nauchno-issledovatel'skiy zhurnal [International Research Journal]. — 2016. — № 10(52). — P. 24–28. [in Russian]

3. Alaee E. Enhancement of neuronal excitability in the medial prefrontal cortex following prenatal morphine exposure / E. Alaee, N. Pachenari, F. Khani, S. Semnanian [et al.] // Brain Research Bulletin. — 2023. — Vol. 204. — P. 110803.

4. Aliyeva N.N. The activity of GABA-T enzyme in the brain of rats in postnatal ontogenesis exposed to hypoxia during fetal period / N.N. Aliyeva // Azerbaijan Journal of Physiology. — 2022. — Vol. 37, № 1. — P. 22–29. — DOI: 10.59883/ajp.4.

5. Al-Nasser M.N. Is L-Glutamate Toxic to Neurons and Thereby Contributes to Neuronal Loss and Neurodegeneration? A Systematic Review / M.N. Al-Nasser, I.R. Mellor, W.G. Carter // Brain Sciences. — 2022. — Vol. 12. — P. 577.

6. Dunn A.D. Molecular and long-term behavioral consequences of neonatal opioid exposure and withdrawal in mice / A.D. Dunn, S.A. Robinson, C. Nwokafor, M. Estill [et al.] // Frontiers in Behavioral Neuroscience. — 2023. — Vol. 17. — P. 1202099. — DOI: 10.3389/fnbeh.2023.1202099.

7. Egbenya D.L. Glutamate receptors in brain development / D.L. Egbenya, E. Aidoo, G. Kyei // Child's Nervous System. — 2021. — Vol. 37. — P. 2753–2758. — DOI: 10.1007/s00381-021-05266-w.

8. Gruenbaum B.F. Glutamate Neurotoxicity and Destruction of the Blood–Brain Barrier: Key Pathways for the Development of Neuropsychiatric Consequences of TBI and Their Potential Treatment Strategies / B.F. Gruenbaum, A. Zlotnik, I. Fleidervish, A. Frenkel [et al.] // International Journal of Molecular Sciences. — 2022. — Vol. 23. — P. 9628. — DOI: 10.3390/ijms23179628.

9. Huang M. Targeting Excitatory Glutamate Receptors for Morphine Tolerance: A Narrative Review / M. Huang, L. Luo, W. Wang, H. Xu [et al.] // CNS Neuroscience & Therapeutics. — 2025. — Vol. 31. — P. e70468. — DOI: 10.1111/cns.70468.

10. Jasper A.H. Glutamatergic Systems and Memory Mechanisms Underlying Opioid Addiction / A.H. Jasper, J. De Vries Taco, P. Jamie // Cold Spring Harbor Perspectives in Medicine. — 2021. — Vol. 11. — P. a039602.

11. Lenin D.O.-de la P. The role of GABA neurotransmitter in the human central nervous system, physiology, and pathophysiology / D.O.-de la P. Lenin, G.-C. Rosario, D´A.-L. Estela [et al.] // Revista Mexicana de Neurociencia. — 2021. — Vol. 22, № 2. — P. 67–76.

12. McAllister J.M. Effects of Prenatal Opioid Exposure on the Brain and Neurodevelopment / J.M. McAllister, S.L. Merhar // Pediatric Clinics of North America. — 2025. — Vol. 72, № 5. — P. 805–823. — DOI: 10.1016/j.pcl.2025.05.012.

13. McGrath T. Emerging Evidence for the Widespread Role of Glutamatergic Dysfunction in Neuropsychiatric Diseases / T. McGrath, R. Baskerville, M. Rogero // Nutrients. — 2022. — Vol. 14. — P. 917.

14. Radhakrishnan R. Neuroimaging in infants with prenatal opioid exposure: current evidence, recent developments and targets for future research / R. Radhakrishnan, G. Grecco, K. Stolze [et al.] // Journal of Neuroradiology. — 2021. — Vol. 48, № 2. — P. 112–120. — DOI: 10.1016/j.neurad.2020.09.009.

15. Ramshini E. Effect of intracerebroventricular injection of GABA receptors antagonists on morphine-induced changes in GABA and Glu transmission within the mPFC: an in vivo microdialysis study / E. Ramshini, H. Alaei, P. Reisi [et al.] // Iranian Journal of Basic Medical Sciences. — 2019. — Vol. 22, № 3. — P. 246–250. — DOI: 10.22038/ijbms.2019.28478.6925.

16. Simmons S.C. Effects of prenatal opioid exposure on synaptic adaptations and behaviors across development / S.C. Simmons, G.G. Grecco, B.K. Atwood // Neuropharmacology. — 2023. — Vol. 222. — P. 109312. — DOI: 10.1016/j.neuropharm.2022.109312.

17. Valeeva G. Excitatory Effects of GABA during Ontogeny / G. Valeeva, R. Khazipov, E.E. Nikolsky // Neuroscience and Behavioral Physiology. — 2013. — Vol. 43, № 5. — P. 656–660. — DOI: 10.1007/s11055-013-9787-z.

18. Wang D. Effect of early embryonic exposure to morphine on defects in the GABAergic system of day-old chicks / D. Wang, J. Jiang, W. Shang [et al.] // Progress in Neuro-Psychopharmacology and Biological Psychiatry. — 2023. — Vol. 121. — P. 110657. — DOI: 10.1016/j.pnpbp.2022.110657.