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CHANGES IN THE ACTIVITY OF ENZYMES RELATED TO GABA METABOLISM IN RATS AS A RESULT OF THE EFFECT OF MORPHINE IN THE PRENATAL STAGE

Research article

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Abstract

The effect of morphine in the prenatal and postnatal stages of ontogenesis is accompanied by significant changes in the amount of GABA in the brain structures. In the presented study, the mechanism of changes in GABA metabolism in the brain structures of rats as a result of the effect of morphine in prenatal ontogenesis was studied.

In accordance with the aim of the study, doses of 2 mg/kg and 10 mg/kg of morphine were used in the organogenesis stage of prenatal ontogenesis. Both doses were injected intraperitoneally into the maternal rats twice a day. The activity of enzymes involved in GABA metabolism — glutamate acid decarboxylase (GAD) and GABA-aminotransferase (GABA-T) — was determined in appropriate laboratory conditions.

The results of the conducted studies showed that a low dose of morphine causes an increase in the activity of the GAD enzyme and a decrease in the activity of the GABA-T enzyme in various structures of the brain of one-month-old offspring of mother rats. The use of high doses of morphine was accompanied by opposite changes in the activity of the enzymes: a decrease in the activity of GAD and an increase in the activity of GABA-T were observed compared to the control group.

The observed changes in the activities of enzymes involved in GABA metabolism depending on the dose of morphine during prenatal ontogenesis clarify the mechanism of changes in the amount of GABA under appropriate conditions and complement the results of previous studies.

Keywords: morphine, prenatal period, gamma-aminobutyric acid, glutamate acid decarboxylase, GABA-aminotransferase.

ИЗМЕНЕНИЕ АКТИВНОСТИ ФЕРМЕНТОВ МЕТАБОЛИЗМА ГАМК У КРЫС, ПОДВЕРГНУТЫХ ВЛИЯНИЮ МОРФИНА В ПРЕНАТАЛЬНОМ ПЕРИОДЕ

Научная статья

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Аннотация

Пренатальное и постнатальное воздействие морфина сопровождается выраженными изменениями содержания ГАМК в структурах головного мозга. В настоящем исследовании изучены механизмы метаболических изменений ГАМК в структурах головного мозга крыс при пренатальном воздействии морфина.

В соответствии с целью исследования, в период органогенеза пренатального онтогенеза применяли морфин в дозах 2 и 10 мг/кг. Препарат вводили самкам крыс внутрибрюшинно два раза в сутки. Активность ферментов метаболизма ГАМК — глутаматдекарбоксилазы (ГДК) и ГАМК-аминотрансферазы (ГАМК-Т) — определяли стандартными биохимическими методами.

Результаты исследования показали, что введение морфина в низкой дозе сопровождалось повышением активности глутаматдекарбоксилазы (ГДК) и снижением активности ГАМК-аминотрансферазы (ГАМК-Т) в различных структурах головного мозга одномесячного потомства крыс. Применение морфина в высокой дозе вызывало противоположные изменения: снижение активности ГДК и повышение активности ГАМК-Т по сравнению с контрольной группой.

Дозозависимые изменения активности ферментов, участвующих в метаболизме ГАМК, в условиях пренатального воздействия морфина объясняют механизмы изменения её содержания в структурах головного мозга и дополняют данные ранее проведённых исследований.

Ключевые слова: морфин, пренатальный период, гамма-аминомасляная кислота, глутаматдекарбоксилаза, ГАМК-аминотрансфераза.

Introduction

Gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter in the central nervous system (CNS), plays an important role in regulating the level of excitability of neurons [8]. The synthesis of GABA occurs mainly through the decarboxylation of glutamate, and this process is catalyzed by the enzyme glutamate acid decarboxylase (GAD). GAD is considered one of the main indicators of the functional state of GABAergic neurons, and changes in its activity directly affect the intensity of synaptic transmission [11]. Therefore, the regulation of GAD is of particular importance in the study of

neurophysiological and neurochemical mechanisms. Another enzyme that plays an important role in GABA metabolism is GABA-T. This enzyme is involved in the degradation of GABA [12].

Opioids, especially morphine, modulate neuronal activity through opioid receptors widely distributed in the CNS [7]. Morphine alters the interactions between dopaminergic, glutamatergic, and GABAergic systems, which can lead to neurotransmitter imbalance [4], [17]. Morphine affects the activity of GABAergic neurons both directly and indirectly, and this effect can be accompanied by changes in the expression and activity of GAD and GABA-T [10].

The prenatal ontogenesis period is a critical stage in the formation of the CNS, and during this period there is a high sensitivity to external influences. Opioid intake during pregnancy can affect the development of neurotransmitter systems in the brain structures of the fetus. It has been noted that the effect of morphine in prenatal ontogenesis causes structural and functional changes in the GABAergic system, including changes in the activity of GAD and GABA-T and GABA levels [6].

Since changes in the activity of GAD and GABA-T determine the intensity of GABA synthesis and degradation, respectively, the study of the mechanism of action of prenatal morphine on these enzymes is of particular relevance. In this regard, the assessment of the activity of GAD and GABA-T under the conditions of application of different doses of morphine in prenatal ontogenesis allows us to clarify the mechanism of neurochemical changes observed in the GABAergic system and is of great importance in explaining the molecular basis of the effect of opioids on the developing brain.

Research methods and principles

The animals used in the experiments consisted of 30 female white rats aged 6 months. The rats were divided into two groups: group I — control animals, group II — morphine-injected animals. The control animals were injected with saline solution into the abdominal cavity. Group II was divided into two subgroups: in the first subgroup, morphine was injected intraperitoneally into the rats at a dose of 2 mg/kg, and in the second subgroup, at a dose of 10 mg/kg. Physiological solution and morphine were administered only during the organogenesis period, on days 8–14 of gestation, twice a day (at 10:00 and 18:00). During the experiment, 1-month-old offspring of all groups were decapitated and their brains were separated into the appropriate structures. The activity of GAD and GABA-T enzymes was determined in brain structures such as the cortex of the cerebral hemispheres, the brain stem, the hypothalamus and the cerebellum [2].

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

Student's t-test was applied to statistically process the experimental results, and statistical analyses were performed using Statistics for Windows and Microsoft Excel programs.

Main results

Changes in GAD activity: Significant changes were observed in the activity of the GAD enzyme as a result of the influence of morphine during prenatal ontogenesis. Thus, intraperitoneal injection of morphine at a dose of 2 mg/kg twice a day in the prenatal period caused a significant increase in GAD activity in the studied structures of the brain. The activity of the enzyme increased by 25% in the cortex of the cerebral hemispheres, 47% in the cerebellum, 38% in the brain stem and 32% in the hypothalamus compared to the control, which indicates that morphine at low doses stimulates enzyme activity in GABAergic neurons. On the contrary, intraperitoneal injection of morphine at a dose of 10 mg/kg twice a day during prenatal ontogenesis caused opposite changes in GAD activity. When comparing these results with the control, it was determined that under appropriate conditions, the activity of GAD decreases by 45% in the cerebral cortex, 52% in the cerebellum, 35% in the brainstem, and 38% in the hypothalamus (table).

Changes in the activity of GABA-T: Intraperitoneal injection of morphine at a dose of 2 mg/kg twice a day in the prenatal period of maternal rats led to a significant decrease in the activity of GABA-T in the studied structures of the brain compared to control values. The activity of the studied enzyme decreased by 17% in the cerebral cortex, 36% in the cerebellum, 27% in the brainstem, and 22% in the hypothalamus, which indicates that low doses of morphine inhibit GABA metabolism through GABA-T. Intraperitoneal administration of morphine at a dose of 10 mg/kg twice daily during prenatal ontogenesis caused opposite changes in the activity of GABA-T. As a result of the effect of the high dose, the activity of the enzyme increased by 39% in the cortex of the cerebral hemispheres, 48% in the cerebellum, 37% in the brainstem, and 33% in the hypothalamus (table).

The results obtained show that the effect of morphine is dose-dependent and that high doses can cause significant changes in the structural functions of the brain by inhibiting GABAergic enzyme activity in the prenatal period. Also, high doses can increase GABA-T activity in the prenatal period, leading to significant modulation processes in GABA metabolism.

Table 1 - Changes in the activity of GABA-related enzymes in various structures of the brain of rats exposed to morphine during organogenesis

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Brain structures	Condition of the experiment	Parameters	17 days	
			GAD (mkmol GABA/q.h)	GABA-T mkmol Glu/q.h
Cortex of the	Control	M±m	71,72±4,35	77,46±3,54

Brain structures	Condition of the experiment	Parameters	17 days	
			GAD (mkmol GABA/q.h)	GABA-T mkmol Glu/q.h
cerebral hemispheres	2 mq/kq, 2 times a day	M±m	89,65±5,72*	64,30±3,68*
		%	125	83
	10 mq/kq, 2 times a day	M±m	39,45±2,56***	107,68±6,55**
		%	55	139
Cerebellum	Control	M±m	85,24±5,70	82,38±4,78
	2 mq/kq, 2 times a day	M±m	125,30±7,15**	52,72±3,60**
		%	147	64
	10 mq/kq, 2 times a day	M±m	40,92±2,64***	121,92±5,75***
		%	48	148
Brain stem	Control	M±m	59,75±2,56	70,65±3,42
	2 mq/kq, 2 times a day	M±m	82,46±4,38**	51,57±2,40**
		%	138	73
	10 mq/kq, 2 times a day	M±m	38,84±1,85***	96,79±4,12**
		%	65	137
Hypothalamus	Control	M±m	94,23±5,16	88,48±3,16
	2 mq/kq, 2 times a day	M±m	124,38±7,50*	69,16±2,40**
		%	132	78
	10 mq/kq, 2 times a day	M±m	58,42±3,35***	117,68±5,68**
		%	62	133

*Note: M±m, n=5; * - p<0.05, ** - p<0.01, *** - p<0.001*

Discussion

The activity of the GAD and GABAT-T enzymes is vital for the normal development of the CNS. GAD directly participates in the formation of synaptic inhibitory signals by converting glutamate to GABA, while GABA-T plays an important role in the metabolism of GABA. If the balance of these enzymes is not correct, key developmental processes such as synaptic excitability, neuronal migration, and network formation may be disrupted, resulting in functional and structural anomalies. Disturbances of the GABAergic system have been associated with various neurodevelopmental disorders and behavioral disorders (e.g., pathology of GABA signaling components). This brings the role of the GABA system to the forefront in neurodevelopmental studies [14].

Opioids, especially morphine, cross the blood-brain barrier and affect neurotransmitter systems, including the functional state of the GABAergic system, through opioid receptors [15], [16]. Prenatal opioid exposure not only affects the formation of synaptic connections, but also alters the mechanisms of synthesis and degradation of neurotransmitters such as glutamate and GABA. Prenatal exposure to morphine can alter the expression and activity of enzymes that control GABA synthesis and lead to long-term changes in GABAergic synaptic transmission, which has the potential to affect neuroplasticity and behavioral functions [15].

Recent studies have shown that prenatal opioid exposure causes various aspects of neurodevelopment — a decrease in brain volume, disruption of structural and functional connections, and changes in synaptic plasticity. These studies show that prenatal opioid exposure can affect not only the migration of nerve cells and the development of neuronal networks, but also the enzymatic regulation of the GABAergic system [9], [15].

Experimental studies have shown that changes in the amount of GABA in brain structures as a result of the influence of various factors depend on the activities of enzymes involved in its metabolism [1], [3], [5]. Also at the metabolic level, prenatal opioid exposure can change the activity of GABA, which is involved in GABA synthesis, and thereby disrupt the GABA/Glu balance, disrupting the mechanisms of synaptic inhibition. The effect of morphine during prenatal ontogenesis can lead to an increase or decrease in GABA levels [13]. These changes in the amount of GABA, as determined in our studies, occur on the basis of a dose-dependent change in the activity of enzymes involved in its metabolism. As a result of the effect of low doses of morphine, the synthesis of GABA increased, and its degradation decreased. As a result, the amount of GABA also increased. As a result of the effect of high doses of morphine, the synthesis of GABA decreased, its degradation increased, and this resulted in a decrease in the amount of GABA.

Since the increase in the activity of the GAD enzyme is one of the main biochemical reasons for the increase in the amount of GABA, this mechanism can be associated with the fact that morphine increases the adaptive inhibitory response to the decrease in the level of excitation in developing neuronal networks. The decrease in the GABA-T enzyme indicates that GABA degradation is weakened, that is, GABA is retained in the tissue for a longer period. This is the second main mechanism of

metabolic enhancement of the inhibitory system. Simmons et al. [18] suggest that prenatal opioid exposure can cause changes in different stages of GABA metabolism, leading to a gradual re-regulation of inhibitory tone. Thus, both increased synthesis (GAD ↑) and decreased catabolism (GABA-T ↓) together explain GABA accumulation, which may result in the enhancement of inhibitory mechanisms during development.

Decreased GAD activity: is the main limiting factor for GABA synthesis. The decrease in GAD enzyme activity observed in our study indicates a direct impairment of GABA synthesis. This change is consistent with the mechanisms described in the literature. Wang et al. [19] also noted a decrease in GAD expression and the number of GABAergic synapses against the background of prenatal morphine exposure. It is highly likely that the decrease in GAD enzyme activity leads to a systemic weakening of inhibitory tone. Thus, the decrease in GABA content is not only due to disruption at the synaptic level, but also to a lack of synthesis at the metabolic level.

Increased GABA-T activity and accelerated GABA catabolism. Increased GABA-T enzyme activity further reduces the level of the inhibitory neurotransmitter by enhancing GABA catabolism. In addition to the biochemical basis of the decrease in GAD synthesis, increased GABA-T activity acts as a maladaptive metabolic mechanism, causing a further decrease in GABA levels.

Conclusion

The effect of morphine at different doses during the organogenesis period of prenatal ontogenesis caused significant changes in the activity of enzymes involved in GABA metabolism in the brain structures of rats. The effect of morphine at low doses is accompanied by an increase in the activity of the GAD enzyme. The effect of morphine at high doses resulted in the formation of opposite changes in the activity of GAD. As a result of the effect of morphine at low doses, a decrease in the activity of the GABA-T enzyme was observed, and as a result of its effect at high doses, an increase was observed. As can be seen, the activity of enzymes involved in the synthesis and breakdown of GABA changes depending on the dose of morphine. These results explain the biochemical mechanisms of the results obtained in previous studies — an increase in the amount of GABA in the brain structures as a result of the effect of morphine at low doses during prenatal ontogenesis, and a decrease in the amount of GABA as a result of its effect at high doses.

Конфликт интересов

Не указан.

Рецензия

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Conflict of Interest

None declared.

Review

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