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Серотонин и циклическая организация сна у здоровых доношенных новорожденных

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Актуальность. Рост психоневрологических заболеваний, обусловленных перинатальной патологией, указывает на необходимость изучения биохимических маркеров поражения мозга новорожденного для своевременной профилактики неблагоприятных последствий. Серотонин в раннем онтогенезе обеспечивает интенсивное развитие нейрональных структур и кортикальных сетей, участвующих в формировании циклической организации сна — тонкого критерия морфофункционального развития мозга.

Цель работы — изучить содержание серотонина у здоровых доношенных новорожденных в сопоставлении с количественной и качественной характеристикой электрополиграфической картины сна.

Материал и методы исследования. Обследовано 84 здоровых новорожденных, которые в зависимости от гестационного возраста разделены на три группы: первая — 37 нед. (20 чел.), вторая — 38 нед. (24 чел.), третья — 39–40 нед. (40 чел.). Содержание серотонина в богатой тромбоцитами плазме крови из вены пуповины и в тромбоцитарной взвеси, приготовленной из венозной крови, взятой у матерей и у детей в первые сутки жизни и повторно на 5-й день, определяли методом высокоэффективной жидкостной хроматографии с электрохимическим детектированием. Проводили количественный и качественный анализ электрополиграммы сна через 7–12 ч после рождения.

Результаты исследования. Содержание серотонина в богатой тромбоцитами плазме в пуповинной крови у детей в 2 раза ниже, чем в венозной крови матерей (0,379 ± 0,116 против 0,756 ± 0,200 мкМ/л), но при этом между показателями существует высокая корреляционная связь (r = 0,8, p < 0,05). При гестационном возрасте 39–40 нед. уровень серотонина в богатой тромбоцитами плазме и в тромбоцитах венозной крови достоверно выше, чем у родившихся в 37 нед. У последних увеличение содержания серотонина в тромбоцитах продолжается после рождения (в первые сутки 0,539 ± 0,149 нМ/10^9 Тг, а на 5-й день — 0,846 ± 0,094 нМ/10^9 Тг; p < 0,05), тогда как показатели у родившихся на 39–40-й неделе гестации не меняются (0,797 ± 0,190 и 0,749 ± 0,142 нМ/10^9 Тг соответственно). Рост содержания серотонина в богатой тромбоцитами плазме и в тромбоцитах ребенка в период с 37-й до 39-й недели как во время внутриутробного развития, так и в первые дни жизни коррелирует с увеличением представленности ортодоксальной фазы сна.

Заключение. Общая закономерность изменений содержания серотонина и циклической организации сна в раннем неонатальном периоде у здоровых новорожденных указывает на возможность использования полученных нормативных значений серотонина в качестве биохимического маркера функционального развития мозга.

Ключевые слова: новорожденные; серотонин; тромбоциты; электрополиграмма сна.

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Serotonin and cyclic sleep organization in healthy full-term newborns

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RELEVANCE: The growth of neuropsychiatric diseases caused by perinatal pathology indicates the need to study the biochemical markers of brain damage in the newborn for the timely prevention of adverse consequences. Serotonin in early ontogenesis provides intensive development of neuronal structures and cortical networks involved in the mechanisms of formation of cyclic sleep organization — a fine criterion of morphofunctional development of the brain.

AIM: The aim of the work is to study the content of serotonin in healthy full-term newborns in comparison with the quantitative and qualitative characteristics of the electropoligraphic sleep pattern.

MATERIAL AND METHODS: 84 healthy newborns were examined, which, depending on the gestational age, were divided into 3 groups: I — 37 weeks (20 people), II — 38 weeks (24 people), III — 39-40 weeks (40 people). The content of serotonin in platelet-rich plasma of blood from the umbilical cord vein and in platelet suspension prepared from venous blood taken from mothers and children on the first day of life and again on day 5 was determined by high-performance liquid chromatography with electrochemical detection. A quantitative and qualitative analysis of the sleep electropoligram was performed 7-12 hours after birth.

RESULTS: The content of serotonin in platelet-rich plasma in umbilical cord blood in children does not depend on the method of birth, is 2 times lower than in the venous blood of mothers (0.379 ± 0.116 microns/l, versus 0.756 ± 0.200 microns/l, but there is a high correlation between the indicators ($r = 0.8$, $p < 0.05$). At the gestational age of 39-40 weeks, the level of serotonin in platelet-rich plasma and in venous blood platelets is significantly higher than in those born at 37 weeks. In the latter, the increase in the content of serotonin in platelets continues after birth (at day 1, 0.539 ± 0.149 nM/10^9 Tr, and on day 5 — 0.846 ± 0.094 nM/10^9 Tr; $p < 0.05$), whereas the indicators for those born at 39-40 weeks of pregnancy. They do not change (0.797 ± 0.190 nM/10^9 Tr and 0.749 ± 0.142 nM/10^9 Tr, respectively). A significant increase in the content of serotonin in the platelet-rich plasma and in the platelets of the child in the period from 37 to 39 weeks, both during intrauterine development and in the first days of life, correlates with an increase in the representation of the orthodox phase in the sleep cycle.

CONCLUSION: The general pattern of changes in serotonin content and cyclic sleep organization in the early neonatal period in healthy newborns, depending on gestational age, indicates the possibility of using the obtained standard values of serotonin as a biochemical marker of functional brain development.

Keywords: newborns; serotonin; platelets; electropolygram; sleep.

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Increase in neurological and mental illnesses associated with exposure to adverse factors during early ontogenesis indicate the need to study the biochemical markers of impaired brain development in newborns to develop early diagnostic methods and prevent long-term effects [1–3]. Experimental and clinical studies have identified the role of brain serotonergic dysfunction in the pathogenesis of various pathologies, such as autism, schizophrenia, and aggressive behavior [4–6]. Serotonin is involved in the differentiation and migration of neurons, formation of interneuronal connections, formation of neuroendocrine functions, motor functions, eating, emotional behavior, memory processes, and learning [7]. The expression of serotonin receptors in the early stages of brain structures in the visual and motor cortex in the perinatal period is 1.5–2 times higher than that in adults, and it is the basis of the polyfunction of serotonin [8]. Serotonin is involved in the formation of the cyclical organization of sleep during early ontogenesis, and the quantitative and qualitative characteristics of the electropoligraphic pattern of sleep are a subtle indicator and universal criterion for evaluating the severity of perinatal brain damage in a child [9]. Comprehensive assessment of the state of the brain's serotonergic system and the cyclical organization of a newborn's sleep can help determine the presence and degree of disorders caused by a perinatal pathology. The most accessible and adequate approach to detect appropriate shifts in serotonin at the brain level is the model of the serotonin system of platelets in human peripheral blood [10]. The available information presented in the literature concerning content serotonin of newborns is contradictory, as previous authors used various methods to determine this parameter, often without taking into consideration the gestational age, clinical condition, and time elapsed since birth of the infant [11–15].

The purpose of this work is to study the content of serotonin in healthy full-term newborns in relation to the quantitative and qualitative characteristics of their electropoligraphic pattern of sleep.

MATERIALS AND METHODS

A total of 84 healthy full-term newborns from healthy mothers whose pregnancies proceeded without complications and whose placenta did not reveal any abnormal pathology were examined. Among the infants, 47 were born through caesarian section and the rest were born vaginally.

Thus, the infants had an average weight of 3,375.00 ± 49.67 g, height of 50.84 ± 0.23 cm, and Apgar score of 8–9. The maximum body weight loss of the infants was 5.91% ± 0.21%, but this weight was restored by days 7–10 of life. The infants were divided into three groups according to gestational age: Group 1 included infants born on week 37 (n = 20), Group 2 included infants born on week 38 (n = 24), and Group 3 included infants born on week 39–40 (n = 40). The morphometric indicators of the infants did not differ significantly among the groups.

Electropolygraphic examination was conducted 7–12 h after birth and included simultaneous electroencephalography (EEG; bipolar frontal-parietal, parietal-occipital, and inter-parietal leads), electrocardiograms in the second standard diversion, electrooculogram, and assessment of breathing and motor activity. The registration time was 1.5–2 h. An EEG instrument "Mizar" (Russia) was used to record electropolygrams. We conducted quantitative and qualitative analyses of the infants' electropoligraphic patterns of sleep according to the accepted method, highlighting the orthodox phase (i.e., calm [non-rapid eye movement {NREM}] sleep), paradoxical (i.e., active [REM] sleep), and the undifferentiated state. The sleep cycle was considered as the time from the beginning of the first orthodox phase to the beginning of the second orthodox phase. In the absence of correlations between EEG, vegetative indicators and behavioral patterns of sleep, including undifferentiated activated and undifferentiated low-activated sleep, were highlighted. Undifferentiated activated sleep was characterized by monotonous polymorphic slow-wave high-amplitude activity on EEG combined with high levels of generalized motor activity, irregular breathing, variable heart rate, and REM. Undifferentiated low-active sleep was characterized by monotonous polymorphic predominantly low-amplitude activity on EEG, a nearly complete lack of motor activity and REM, regular breathing, and a monotonous heart rate.

Serotonin content was determined in platelet-rich plasma (PRP) obtained from the venous blood of the umbilical cord after the birth of the child (64 samples), and in platelet suspension, prepared from venous blood (72 samples), taken in the first day of life, and in 19 children again on the 5th day. The level of serotonin in the PRP and platelet suspension of venous blood were determined in nine mothers before cesarean section at weeks 39–40 of pregnancy.

From the blood by centrifuge prepared PRP, it counted the number of platelets. Platelet suspension was obtained from PRP. The content of serotonin in platelets was determined by dividing by the number of platelets.

The amount of serotonin was determined by highly effective liquid chromatography with electrochemical detection. Chromatographic analysis was performed on a Reprosil 80 ODS-2 column (100×4 mm, 3 microns, Dr. Maisch GmbH, Germany), and detection was performed in an analytical cell of a 510A Coulochem II instrument (ESA, USA) with a potential of 0.65 V.

Statistical analysis was conducted using Statistica 6 software (StatSoft, Inc., USA). The descriptive statistics

included average arithmetic (*M*), average quadratic deviation (σ), and average error (*m*). The validity of differences between the averages of parameters was determined by the Mann–Whitney *U* criterion. The critical level was considered at ≤0.05.

RESULTS AND DISCUSSION

Studies have shown that healthy full-term infants in the first day of life show a clear differentiation of sleep phases. The orthodox phase usually begins after the paradoxical phase. During this period, EEG shows generalized high-amplitude oscillations, alternating with areas of a relatively flat curve. Slow waves make up 20.2% of the total wave, which is dominated by vibrations of 4–6 per second and amplitudes of up to 40 microns. Motor activity is reduced and makes up only 7.3% of the duration of the phase. Generalized reactions are recorded once in every 2 min of the phase and last on average 9.6 ± 1.9 s; local movements are absent. The transition from the orthodox phase to the paradoxical phase of sleep is rapid; for example, the EEG shows a decrease in slow-wave amplitude within 20–30 s. The infant may show disturbed breathing regularity, sharp movements, and, sometimes, short-term awakening. The EEG obtained during the paradoxical phase of sleep is fairly distinct, indicating irregular breathing, heart rhythm, and oculomotor activity. The total period of motor activity is 33.6% of the duration of the phase, with 81.7% of the time of all movements occupied by generalized reactions with an average duration of 29.5 ± 4.3 s. Local movements of the head, arms, legs, and face, which are typical phenomena of the paradoxical phase of sleep, are recorded as often as generalized reactions, but they last 3.8 ± 0.3 s. A representation of the orthodox phase of sleep with increasing gestational age is depicted in Table 1.

The serotonin content in newborns does not depend on the method of birth, which was the basis for combining data in each group (Table 2). The serotonin content of those born at 39–40 weeks was significantly higher than that in infants born at 37 weeks. Serotonin levels in the venous-blood PRP of nine mothers in the third group were 0.756 ± 0.200 mcmol/l. Serotonin levels in the cord-blood PRP taken after birth were approximately half (i.e., 0.379 ± 0.116 mcmol/l) those in venous-blood PRP, but a high correlation between these indicators was observed ($r = 0.8$; $p < 0.05$).

The highest levels of serotonin in platelets were noted in infants born naturally on week 39 (Table 3). Platelets at this point of intrauterine development were clearly higher than those observed on weeks 37 and 38. The serotonin contents in the platelets of mothers of the third group and in the first days of their children's lives were 1.849 ± 0.334 and 0.718 ± 0.198 nmol/10^9 Tr, respectively ($p < 0.01$); the correlation between these indicators was weak ($r = 0.5$; $p > 0.05$).

The increase in serotonin in platelets of infants with a gestational age of 37–38 weeks continued after birth (first day, 0.539 ± 0.149 nmol/10^9 Tr; fifth day, 0.846 ± 0.094 nmol/10^9 Tr; $p < 0.05$), but the serotonin contents of those born on weeks 39 and 40 did not change significantly (0.797 ± 0.190 and 0.749 ± 0.142 nmol/10^9 Tr, respectively).

Thus, between the 37th and 39th week, the content of serotonin in the PRP and platelets of an infant increased significantly both during fetal development and after birth in the first days of life, which coincides with the change in the orthodox phase of the sleep cycle. This same dynamic has been observed in premature and full-term infants [16, 17]. A number of researchers attributed the high levels of serotonin observed in infants in their first week, month, and year of life [15, 18] to the maturation of enzymes involved in its synthesis [13], as well as the increase in the production of enterochromophin cells in the intestine [19].

The infant receives increasing doses of maternal serotonin from the embryonic period of development to birth [20, 21]. The mother's platelets deliver serotonin to the inter -pile space, where it is secreted by exocytosis and captured by trophoblasts. Serotonin enters the vorsina chorion through syncytiotrophoblasts and then travels to

Table 1. Duration of phases and sleep cycle in infants of different gestational ages

Group	Sleep phase, s		Sleep cycle, s
	Orthodox	Paradoxical	
First ($n = 6$)	17.00 ± 0.78	25.25 ± 0.76	40.50 ± 1.44
Second ($n = 12$)	20.80 ± 0.96	31.40 ± 5.33	52.0 ± 5.47
Third ($n = 19$)	21.26 ± 0.68	29.4 ± 4.06	51.9 ± 4.23
p_1	0.03	>0.05	>0.05
p_2	0.01	>0.05	>0.05
p_3	>0.05	>0.05	>0.05

Note. The validity of the differences between the first and second groups is p_1, that between the first and third groups is p_2, and that between the second and third groups is p_3.

Table 2. Serotonin content (μmol/l) in the platelet-rich plasma of newborns of different gestational ages born by cesarean section (A) and naturally (B)

Subgroup	Group			Significance of differences p_1 p_2 p_3
	I (*n* = 18)	II (*n* = 19)	III (*n* = 27)	
A (*n* = 41)	0.253 ± 0.044 *n* = 15	0.431 ± 0.080 *n* = 15	0.561 ± 0.139 (*n* = 11)	>0.05 <0.05 >0.05
B (*n* = 23)	0.399 ± 0.204 (*n* = 3)	0.476 ± 0.084 (*n* = 4)	0.484 ± 0.089 (*n* = 16)	>0.05 >0.05 >0.05
p	>0.5	>0.5	>0.5	
A + B (*n* = 64)	0.277 ± 0.048 *n* = 18	0.440 ± 0.065 (*n* = 19)	0.516 ± 0.076 (*n* = 27)	>0.05 **<0.05** >0.05

Note. Validity of differences: *p* — between subgroups A and B; p_1 — between the first and second groups; p_2 — between the first and third groups; p_3 — between the second and third groups.

Table 3. Serotonin content (nmol/10^9 Tr) in the venous-blood platelets of infants of different gestational ages born by cesarean section (A) and naturally (B)

Subgroup	Group			Significance of differences p_1 p_2 p_3
	I (*n* = 14)	II (*n* = 20)	III (*n* = 38)	
A (*n* = 40)	0.481 ± 0.163 (*n* = 11)	0.417 ± 0.097 (*n* = 15)	0.668 ± 0.140 (*n* = 14)	>0.05 <0.05 >0.05
B (*n* = 32)	0.402 ± 0.059 (*n* = 3)	0.519 ± 0.107 (*n* = 5)	0.886 ± 0.082 (*n* = 24)	>0.05 >0.05 >0.05
p	0.5	0.5	0.01	
A + B (*n* = 72)	0.464 ± 0.127 (*n* = 14)	0.483 ± 0.076 (*n* = 20)	0.806 ± 0.074 (*n* = 38)	>0.05 = 0.01 = 0.01

Note. Validity of differences: p_1 — between the first and second groups; p_2 — between the first and third groups; p_3 — between the second and third groups.

the cytotrophoblasts and capillaries of the fetal part of the placenta; transporters in the syncytiotrophoblast control the amount of serotonin transmitted [22]. Serotonin is a major product of tryptophan metabolism and the placenta; the enzymes tryptophan hydroxylase 1 and 2 are involved in this process [23, 24]. Numerous experimental studies have shown that the placenta is the main source of serotonin during the early development of the fetal anterior brain [25]. In the first and early-second trimester of pregnancy, exogenous serotonin from the placenta promotes cortical neurogenesis, migration, and the launch of axonal pathways, which modulates neuronal brain development even before the production of cerebral serotonin. Receptors, transporters, and enzymes for the synthesis of the substance are available in the brain well before the development of serotonin inertia [26]. Serotonergic neurons in the fetal brain initially appear in the stem, especially in the dorsal and medial nuclei of the stem; by the 15th week, their projections are observed in the cortex and hippocampus [27]. Beginning in the second trimester of pregnancy, a shift toward the effects of endogenous cerebral serotonin from the dorsal neurons of the seam may be observed, but the delivery of placental serotonin continues [26].

According to the results of our studies, the serotonin content in the PRP and platelets of infants directly depends on the serotonin level of their mother's blood but remains lower than that of the latter. The rapid increase (by the fifth day of life) in serotonin content in the platelets of children born earlier than the 39th week of gestation may be due to the activation of their brain serotonergic system as a result of exposure to new environmental factors. Cerebral serotonin in the first days of life freely passes through the blood–brain barrier and is a significant source of serotonin in the peripheral blood [28]. Increases in the production of cerebral serotonin in this short period of ontogenesis promote the intensive development of neuronal structures and cortical networks, especially the sensory cortex, the middle brain, the thalamus, and the dorsal nuclei of the brain stem, all of which are involved in the mechanisms of the regulation of .circadian rhythm [29]. Serotonin, because of the diversity of its synthesizing cells, the high branching of their axons, and its large number of receptors (at least 15 types and subtypes), plays important roles in the regulation of wakefulness and the beginning of the orthodox phase of sleep [30].

Our research showed that increases in serotonin content in infants born in the 37th week of gestation increase

the duration of the orthodox phase of sleep, during which homeostatic regulation and synchronization of intersystemal interactions occur; these changes optimize the adaptation and further development of the newborn's brain [31].

Similar changes in the structure of sleep are observed in infants in the last 2–3 weeks of intrauterine development; these changes are believed to determine the optimal regulation of cardiac activity and breathing during birth and adaptation to new environments [32].

CONCLUSION

Evaluation of serotonin content in healthy full-term infants in relation to the quantitative and qualitative characteristics of their electropoligraphic patterns of sleep could help establish a general pattern of changes in the early neonatal period according to gestational age. The results of this study indicate the possibility of using normative values of serotonin as a biochemical marker of disorders of functional brain development.

СПИСОК ЛИТЕРАТУРЫ

1. Huang L., Yu X., Keim S. et al. Maternal prepregnancy obesity and child neurodevelopment in the Collaborative Perinatal Project // Int. J. Epidemiol. 2014. Vol. 43. No. 3. P. 783–792. doi: 10.1093/ije/dyu030

2. Van Lieshout R.J., Voruganti L.P. Diabetes mellitus during pregnancy and increased risk of schizophrenia in offspring: a review of the evidence and putative mechanisms // J. Psychiatry Neurosci. 2008. Vol. 33. No. 5. P. 395–404.

3. Olfson M., Blanco C., Wang S., Laje G., Correll C.U. National trends in the mental health care of children, adolescents, and adults by office-based physicians // JAMA Psychiatry. 2014. Vol. 71. No. 1. P. 81–90. doi: 10.1001/jamapsychiatry.2013.3074

4. Jenkins T.A., Nguyen J.C., Polglaze K.E., Bertrand P.P. Influence of tryptophan and serotonin on mood and cognition with a possible role of the Gut-Brain Axis // Nutrients. 2016. Vol. 8. No. 1. P. 56. doi: 10.3390/nu8010056

5. Edlow A.G. Maternal obesity and neurodevelopmental and psychiatric disorders in offspring // Prenat. Diagn. 2017. Vol. 37. No. 1. P. 95–110. doi: 10.1002/pd.4932

6. Kepser L.J., Homberg J.R. The neurodevelopmental effects of serotonin: a behavioural perspective // Behav. Brain Res. 2015. Vol. 277. P. 3–13. doi: 10.1016/j.bbr.2014.05.022

7. Uzbekov M.G., Murphy S., Rose S.P. Ontogenesis of serotonin 'receptors' in different regions of rat brain // Brain Res. 1979. Vol. 168. No. 1. P. 195–199. doi: 10.1016/0006-8993(79)90139-2

8. Попова Н.К., Куликов А.В. Многообразие серотонинергических рецепторов как основа полифункциональности серотонина // Успехи функциональной нейрохимии: сборник статей. Санкт-Петербург, 2003. С. 56–73.

9. Евсюкова И.И. Формирование циклической организации сна в раннем онтогенезе при различных условиях внутриутробного развития ребенка // Российский физиологический журнал им. И.М. Сеченова. 2013. Т. 99. № 2. С. 166–174.

10. Oreland L., Hallman J. Blood platelets as a peripheral marker for the central serotonin system // Nordisk Psykiatrisk Tidsskrift. 1989. Vol. 43. Suppl. 20. P. 43–51. doi: 10.3109/08039488909100833

11. Tu J.B., Wong C.Y. Serotonin metabolism in normal and abnormal infants during the perinatal period // Biol. Neonate. 1976. Vol. 29. No. 3–4. P. 187–193. doi: 10.1159/000240863

12. Berman J.L., Justice P., Hsia D.Y. The metabolism of 5-hydroxytryptamin (serotonin) in the newborn // J. Pediatr. 1965. Vol. 67. No. 4. P. 603–608. doi: 10.1016/s0022-3476(65)80431-0

13. Hazra M., Benson S., Sandler M. Blood 5-hydroxytryptamine levels in the newborn // Arch. Dis. Child. 1965. Vol. 40. No. 213. P. 513–515. doi: 10.1136/adc.40.213.513

14. Anderson G.M., Czarkowski K., Ravski N., Epperson C.N. Platelet serotonin in newborns and infants: ontogeny, heritability, and effect of *in utero* exposure to selective serotonin reuptake inhibitors // Pediatr. Res. 2004. Vol. 56. No. 3. P. 418–422. doi: 10.1203/01.PDR.0000136278.23672.A0

15. Flachaire E., Beney C., Berthier A. et al. Determination of reference values for serotonin concentration in platelets of healthy newborns, children, adults, and elderly subjects by HPLC with electrochemical detection // Clin. Chem. 1990. Vol. 36. No. 12. P. 2117–2120. doi: 10.1093/clinchem/36.12.2117

16. Клименко Т.М., Кварацхелия Т.М., Водяницкая С.В. Изменения в легких и катехоламиновый статус при спинальной родовой травме у новорожденных // Здоровье ребенка. 2007. № 3(6). С. 41–43.

17. Шейбак Л.Н., Каткова Е.В. Серотонин и его производные в сыворотке пуповинной крови недоношенных новорожденных детей // Российский вестник перинатологии и педиатрии. 2010. Т. 55. № 4. С. 27–30.

18. De Villard R., Flachaire E., Laujin A. et al. Etude de la concentration en sérotonine plaquettaire chez les enfants de moins de 5 ans [Platelet serotonin concentration in children under 5 years of age] // Pediatrie. 1991. Vol. 46. No. 12. P. 813–816.

19. Mashige F., Matsushima Y., Kanazawa H. et al. Acidic catecholamine metabolites and 5-hydroxyindoleacetic acid in urine: the influence of diet // Ann. Clin. Biochem. 1996. Vol. 33. Pt. 1. P. 43–49. doi: 10.1177/000456329603300106

20. Field T., Diego M., Hernandez-Reif M. et al. Prenatal serotonin and neonatal outcome: brief report // Infant. Behav. Dev. 2008. Vol. 31. No. 2. P. 316–320. doi: 10.1016/j.infbeh.2007.12.009

21. Rosenfeld C.S. Placental serotonin signaling, pregnancy outcomes, and regulation of fetal brain development† // Biol. Reprod. 2020. Vol. 102. No. 3. P. 532–538. doi: 10.1093/biolre/ioz204

22. Kliman H.J., Quaratella S.B., Setaro A.C. et al. Pathway of maternal serotonin to the human embryo and fetus // Endocrinology. 2018. Vol. 159. No. 4. P. 1609–1629. doi: 10.1210/en.2017-03025

23. Laurent L., Deroy K., St-Pierre J., Côté F., Sanderson J.T., Vaillancourt C. Human placenta expresses both peripheral and neuronal isoform of tryptophan hydroxylase // Biochimie. 2017. Vol. 140. No. 159–165. doi: 10.1016/j.biochi.2017.07.008

24. Ranzil S., Walker D.W., Borg A.J., Wallace E.M., Ebeling P.R., Murthi P. The relationship between the placental serotonin pathway and fetal growth restriction // Biochimie. 2019. Vol. 161. P. 80–87. doi: 10.1016/j.biochi.2018.12.016
25. Bonnin A., Goeden N., Chen K. et al. A transient placental source of serotonin for the fetal forebrain // Nature. 2011. Vol. 472. No. 7343. P. 347–350. doi: 10.1038/nature09972
26. Bonnin A., Levitt P. Fetal, maternal, and placental sources of serotonin and new implications for developmental programming of the brain // Neuroscience. 2011. Vol. 197. P. 1–7. doi: 10.1016/j.neuroscience.2011.10.005
27. Zhou F.C., Sari Y., Zhang J.K. Expression of serotonin transporter protein in developing rat brain // Brain Res. Dev. Brain Res. 2000. Vol. 119. No. 1. P. 33–45. doi: 10.1016/s0165-3806(99)00152-2
28. Nasyrova D.I., Sapronova A.Y., Balbashev A.V. et al. Development of central and peripheral serotonin-producing systems in rats in ontogenesis // J. Evol. Biochem. Phys. 2009. Vol. 45. No. 1. P. 78–85. doi: 10.1134/S0022093009010074
29. Peirano P., Algarín C., Uauy R. Sleep-wake states and their regulatory mechanisms throughout early human development // J. Pediatr. 2003. Vol. 143. No. 4. Suppl. P. S70–S79. doi: 10.1067/s0022-3476(03)00404-9
30. Ковальзон В.М. Основы сомнологии. Физиология и нейрохимия цикла бодрствование – сон. Москва, 2011.
31. Евсюкова И.И., Федорова М.В. Особенности кардиоинтервалограммы во время сна у новорожденных детей // Физиология человека. 2005. Т. 31. № 1. С. 33–38.
32. Poblano A., Haro R., Arteaga C. Neurophysiologic measurement of continuity in the sleep of fetuses during the last week of pregnancy and in newborns // Int. J. Biol. Sci. 2007. Vol. 4. No. 1. P. 23–28. doi: 10.7150/ijbs.4.23

REFERENCES

1. Huang L, Yu X, Keim S, et al. Maternal prepregnancy obesity and child neurodevelopment in the Collaborative Perinatal Project. *Int J Epidemiol*. 2014;43(3):783–792. doi: 10.1093/ije/dyu030
2. Van Lieshout RJ, Voruganti LP. Diabetes mellitus during pregnancy and increased risk of schizophrenia in offspring: a review of the evidence and putative mechanisms. *J Psychiatry Neurosci.* 2008;33(5):395–404.
3. Olfson M, Blanco C, Wang S, Laje G, Correll CU. National trends in the mental health care of children, adolescents, and adults by office-based physicians. *JAMA Psychiatry*. 2014;71(1):81–90. doi: 10.1001/jamapsychiatry.2013.3074
4. Jenkins TA, Nguyen JC, Polglaze KE, Bertrand PP. Influence of tryptophan and serotonin on mood and cognition with a possible role of the Gut-Brain Axis. *Nutrients*. 2016;8(1):56. doi: 10.3390/nu8010056
5. Edlow AG. Maternal obesity and neurodevelopmental and psychiatric disorders in offspring. *Prenat Diagn*. 2017;37(1):95–110. doi: 10.1002/pd.4932
6. Kepser LJ, Homberg JR. The neurodevelopmental effects of serotonin: a behavioural perspective. *Behav Brain Res*. 2015;277:3–13. doi: 10.1016/j.bbr.2014.05.022
7. Uzbekov MG, Murphy S, Rose SP. Ontogenesis of serotonin 'receptors' in different regions of rat brain. *Brain Res*. 1979;168(1):195–199. doi: 10.1016/0006-8993(79)90139-2
8. Popova NK, Kulikov AV. Mnogoobrazie serotoninergicheskih receptorov kak osnova polifunkcional'nosti serotonina. *Uspehi funkcional'noj nejrohimii: sbornik statej*. Saint Petersburg; 2003. P. 56–73. (In Russ.)
9. Evsyukova II. The cyclic organization of sleep in early ontogenesis in different conditions of intrauterine fetus development. *Russian Journal of Physiology*. 2013;9(2):166–174. (In Russ.)
10. Oreland L, Hallman J. Blood platelets as a peripheral marker for the central serotonin system. *Nordisk Psykiatrisk Tidsskrift*. 1989;43(Suppl. 20):43–51. doi: 10.3109/08039488909100833
11. Tu JB, Wong CY. Serotonin metabolism in normal and abnormal infants during the perinatal period. *Biol Neonate*. 1976;29(3–4):187–193. doi: 10.1159/000240863
12. Berman JL, Justice P, Hsia DY. The metabolism of 5-hydroxytryptamin (serotonin) in the newborn. *J Pediatr.* 1965;67(4):603–608. doi: 10.1016/s0022-3476(65)80431-0
13. Hazra M, Benson S, Sandler M. Blood 5-hydroxytryptamine levels in the newborn. *Arch Dis Child*. 1965;40(213):513–515. doi: 10.1136/adc.40.213.513
14. Anderson GM, Czarkowski K, Ravski N, Epperson CN. Platelet serotonin in newborns and infants: ontogeny, heritability, and effect of *in utero* exposure to selective serotonin reuptake inhibitors. *Pediatr Res.* 2004;56(3):418–422. doi: 10.1203/01.PDR.0000136278.23672.A0
15. Flachaire E, Beney C, Berthier A, et al. Determination of reference values for serotonin concentration in platelets of healthy newborns, children, adults, and elderly subjects by HPLC with electrochemical detection. *Clin Chem*. 1990;36(12):2117–2120. doi: 10.1093/clinchem/36.12.2117
16. Klimenko T, Kvaratsheliya T, Vodjanitskaya S. Changes in lungs and catecholamine status in the case of spinal intranatal trauma in newborns. *Zdorovie rebenka*. 2007;3(6):41–43. (In Russ.)
17. Sheibak LN, Katkova EV. Serotonin and its derivatives in the umbilical cord blood serum of premature newborn infants. *Rossijskij vestnik perinatologii i pediatrii*. 2010;55(4):27–30. (In Russ.)
18. De Villard R, Flachaire E, Laujin A, et al. Etude de la concentration en sérotonine plaquettaire chez les enfants de moins de 5 ans [Platelet serotonin concentration in children under 5 years of age]. *Pediatrie.* 1991;46(12):813–816.
19. Mashige F, Matsushima Y, Kanazawa H, et al. Acidic catecholamine metabolites and 5-hydroxyindoleacetic acid in urine: the influence of diet. *Ann Clin Biochem*. 1996;33(Pt 1):43–49. doi: 10.1177/000456329603300106
20. Field T, Diego M, Hernandez-Reif M, et al. Prenatal serotonin and neonatal outcome: brief report. *Infant Behav Dev*. 2008;31(2):316–320. doi: 10.1016/j.infbeh.2007.12.009
21. Rosenfeld CS. Placental serotonin signaling, pregnancy outcomes, and regulation of fetal brain development. *Biol Reprod*. 2020;102(3):532–538. doi: 10.1093/biolre/ioz204

22. Kliman HJ, Quaratella SB, Setaro AC, et al. Pathway of maternal serotonin to the human embryo and fetus. *Endocrinology*. 2018;159(4):1609–1629. doi: 10.1210/en.2017-03025
23. Laurent L, Deroy K, St-Pierre J, Côté F, Sanderson JT, Vaillancourt C. Human placenta expresses both peripheral and neuronal isoform of tryptophan hydroxylase. *Biochimie*. 2017;140:159–165. doi: 10.1016/j.biochi.2017.07.008
24. Ranzil S, Walker DW, Borg AJ, Wallace EM, Ebeling PR, Murthi P. The relationship between the placental serotonin pathway and fetal growth restriction. *Biochimie*. 2019;161:80–87. doi: 10.1016/j.biochi.2018.12.016
25. Bonnin A, Goeden N, Chen K, et al. A transient placental source of serotonin for the fetal forebrain. *Nature*. 2011;472(7343):347–350. doi: 10.1038/nature09972
26. Bonnin A, Levitt P. Fetal, maternal, and placental sources of serotonin and new implications for developmental programming of the brain. *Neuroscience*. 2011;197:1–7. doi: 10.1016/j.neuroscience.2011.10.005
27. Zhou FC, Sari Y, Zhang JK. Expression of serotonin transporter protein in developing rat brain. *Brain Res Dev Brain Res*. 2000;119(1):33–45. doi: 10.1016/s0165-3806(99)00152-2
28. Nasyrova DI, Sapronova AY, Balbashev AV, et al. Development of central and peripheral serotonin-producing systems in rats in ontogenesis. *J Evol Biochem Phys*. 2009;45(1):78–85. doi: 10.1134/S0022093009010074
29. Peirano P, Algarín C, Uauy R. Sleep-wake states and their regulatory mechanisms throughout early human development. *J Pediatr*. 2003;143(4 Suppl.):S70-S79. doi: 10.1067/s0022-3476(03)00404-9
30. Kovalson VM. Osnovi somnologii. Fiziologiya i neurochimiya zikla bodrstvovanie-son. Moscow; 2011. (In Russ.)
31. Evsyukova II, Kondrat'eva MV. Characteristics of the cardiointervalogram in newborns during sleep. *Human Physiology*. 2005;31(2):199–203. (In Russ.)
32. Poblano A, Haro R, Arteaga C. Neurophysiologic measurement of continuity in the sleep of fetuses during the last week of pregnancy and in newborns. *Int J Biol Sci*. 2007;4(1):23–28. doi: 10.7150/ijbs.4.23

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