ISSN 0022-0930, Journal of Evolutionary Biochemistry and Physiology, 2024, Vol. 60, No. 5, pp. 1677–1684. © Pleiades Publishing, Ltd., 2024.

EXPERIMENTAL PAPERS

Neonatal Hypoxia Induces Behavioral Deficit Associated with Impaired Glucocorticoid and Serotoninergic Systems in Adult Rats

E. I. Tyulkova[a],*, V. A. Stratilov[a], and O. V. Vetrovoy[a]

[a] *Pavlov Institute of Physiology, Russian Academy of Sciences, St. Petersburg, Russia*
**e-mail: etyulkova@yandex.ru*

Received July 29, 2024; revised August 6, 2024; accepted August 6, 2024

Abstract—We investigated plasma concentrations of adrenocorticotropic hormone (ACTH), corticosterone and serotonin in juvenile and adult rats, as well as raphe serotonin levels and behavioral responses in the open field and elevated plus maze tests in adult rats, exposed to three sessions of neonatal hypobaric hypoxia (360 mm Hg, 2 h each, once a day) within days 8–10 postpartum. This noninvasive rat model of neonatal hypoxia (NH) simulates mild perinatal hypoxic injury in human fetuses and premature infants. At 3 months of age, NH-exposed rats exhibited reduced exploratory behavior and increased anxiety in both behavioral tests, accompanied by decreased serotonin levels in the raphe nuclei. In adult NH-exposed rats, plasma corticosterone and serotonin levels remained unaltered, while ACTH levels showed a significant decrease. Our findings suggest that early postnatal hypoxic stress disrupts the serotoninergic system and modifies the hypothalamic–pituitary–adrenocortical axis, leading to long-lasting behavioral deficits in adult rats.

DOI: 10.1134/S0022093024050016

Keywords: rats, neonatal hypoxia, glucocorticoid system, serotonin system, behavior

INTRODUCTION

One of the key challenges of modern perinatology is hypoxic-ischemic encephalopathy. This disease occurs most often in newborns with perinatal asphyxia. Over the past 30 years, the number of preterm births has increased by 20%. The premature infant primarily experiences hypoxic exposures due to underdeveloped lungs [1]. During labor, umbilical cord entanglement or abnormal amniotic fluid can cause fetal distress, asphyxia and hypoxia. Hypoxia-ischemia impairs the formation of newborn's central motor pathways and may affect the normal development of brain plasticity [2]. The increased susceptibility of periventricular white matter to hypoxia-ischemia in premature infants also predisposes to motor, cognitive and sensory deficits. Cognitive impairments and atypical brain development are thought to be consequences of preterm and/or obstructed labor.

In rodents (rats, mice), days 7–10 postpartum coincide with the most common terms of premature human pregnancy. Similar to a human fetus at 34 weeks of gestation, the brain growth in rodents peaks at the age of 7 days, followed by cortical myelination [3]. At this time, the programmed histogenetic processes of proliferation, migration and differentiation of all the structural elements of nervous tissue are completed, neocortical layers undergo shaping and ordering, while synapto- and angiogenesis are under way. The most frequently used current model of hypoxic-ischemic encephalopathy is the

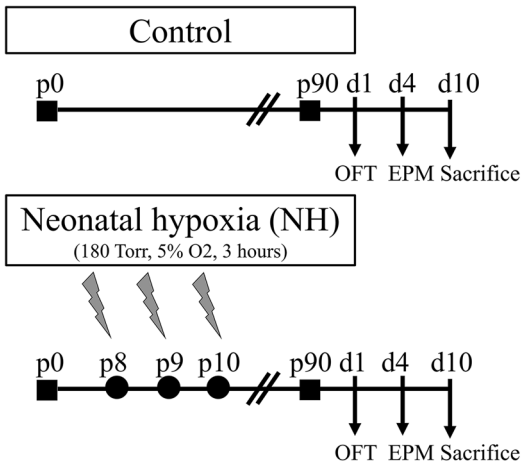

Fig. 1. Study design. NH—neonatal hypoxia; p0—birthday; p8, p9, p10, p90—postnatal days; d1, d4, d10—experimental days; OFT—open field test; EPM—elevated plus maze test.

Rice–Vannucci's [4, 5] that includes two stages, right common carotid artery ligation followed by hypoxic exposure to a gas mixture. This model, which simulates neonatal hypoxia-ischemia, leads to neurological disorders, as confirmed by a series of behavioral assessments, such as the Zea Longa and neurological severity scores, as well as the Morris water maze, Y-maze, rotarod, and negative geotaxis tests [6]. Although premature pregnancy not always combines with traumatic brain injury, almost all premature infants experience hypoxia of varying severity, which may also entail neurodevelopmental reprogramming. Therefore, purely hypoxic early neonatal exposures are also widely employed in addition to the Rice-Vannucci's model. The use of hypoxia between days 6 and 12 postpartum, which is a critical period for brain development (synaptic maturation period) and vulnerability to hypoxic exposures, can lead to various disorders [7, 8]. This model can reproduce the consequences of chronic or repetitive hypoxia, which may arise under certain clinical conditions, such as chronic lung disease in premature infants or sleep apnea. The physiological and pathological processes, this model is intended to reproduce, may include repetitive hypoxic effects on brain development, neuronal damage, and potential long-term neurologic deficits. The model may be applicable when studying such conditions as perinatal asphyxia and other hypoxia-induced neonatal brain injuries [7, 8].

Intermittent hypoxia experienced in the first days postpartum is a common stressor in preterm neonates [9]. Neonatal stressors can have long-term programming/reprogramming effects on the developing brain, and the aftereffects of such a remodeling may persist in adulthood. The early neonatal exposure to hypobaric hypoxia within the first days postpartum has been shown to result in more pronounced impairments in exploratory behavior, cognitive deficits, and dopaminergic system's modification compared to normobaric hypoxia [10, 11]. We hypothesized that intermittent hypobaric hypoxia experienced on days 8–10 of postnatal ontogenesis may induce a stress response and thus modify glucocorticoid system's activity in juvenile and adult rats. So, this study was aimed to investigate the aftereffects of hypobaric neonatal hypoxia (NH, 360 mm Hg, three 2-h sessions at 24-h intervals) in the period between day 8 and day 10 postpartum on plasma levels of adrenocorticotropic hormone (ACTH), corticosterone and serotonin in juvenile and adult rats, as well as behavior and serotonin levels in the raphe nuclei of adult rats.

MATERIALS AND METHODS

Animals. The study was carried out on animals from the Center for Collective Use "Biocollection of Laboratory Mammals of Different Taxonomic Affiliation" of Pavlov Institute of Physiology, Russian Academy of Sciences. Pavlov Institute of Physiology of the Russian Academy of Sciences. There were used adult pregnant female Wistar rats (aged 12–13 weeks, 220–250 g) and their offspring.

Immediately prior to the birth of offspring, pregnant rats were set apart into individual cages, and each litter was kept separately later on. After weaning, male rats were placed into cages measuring 60 × 30 × 20 cm, by 6 animals per cage. To minimize litter inequality, each group of rats was composed of randomly selected animals born to different mothers. The rats ad libitum access to food (dry pelleted feed produced at a feed mill in Tosno, Leningrad Region) and water, and were kept under a 12 h/12 h dark/light cycle at a room temperature and a constant humidity of about 60%.

Experimental design. The experiments were carried out on male rat pups (Fig. 1). A half of the rats were exposed to three sessions of hypobaric hypoxia (neonatal hypoxia, NH). To create NH on postnatal days

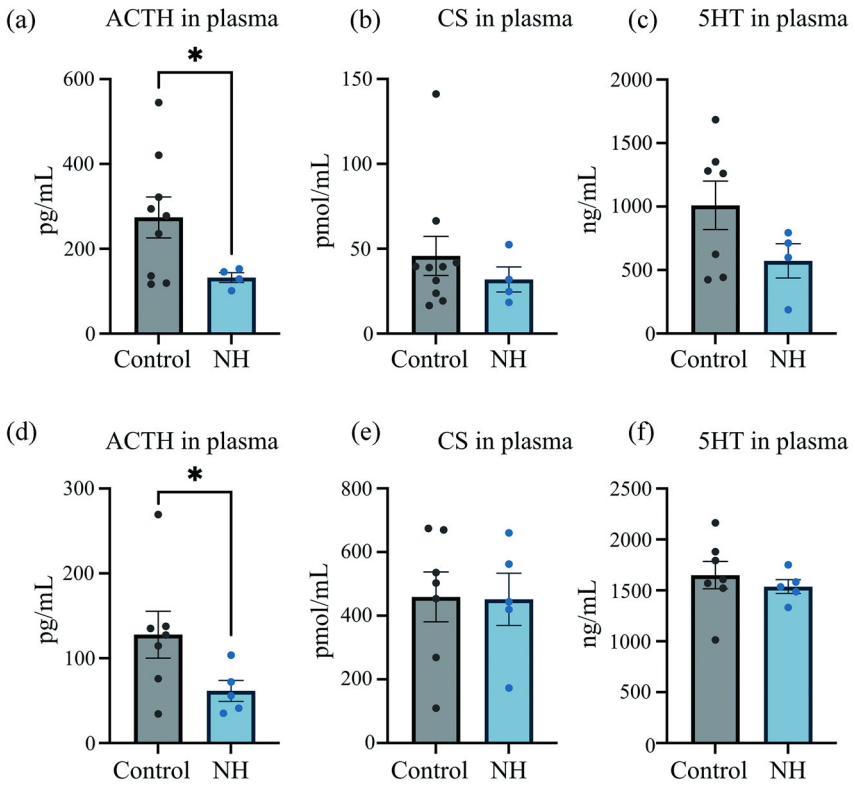

Fig. 2. Effects of neonatal hypoxia (NH) on plasma concentrations of ACTH (a, d), corticosterone (b, e), and serotonin (c, f) in 2-week-old and 3-month-old rats ($n = 5–7$). * Significant differences vs. control group, $p < 0.05$ (Welch's t-test).

8, 9 and 10, the rats were placed into a flow-type hypoxic chamber, and the pressure was gradually reduced to 360 mm Hg, which corresponds to 10% of normobaric oxygen. Each session lasted 2 h, the inter-session interval was 24 h. After each exposure, the rats were returned to the maternal cage. To standardize conditions, control animals were also placed into a hypoxic chamber according to a similar protocol, albeit without subsequent pressure reduction. We have previously used this model to test the hypothesis of possible reprogramming the effects of prenatal hypoxia on days 14–16 of gestation [12].

Immunoenzymatic assays. Using commercial ELISA kits, plasma levels of adrenocorticotropic hormone (ACTH) (ab263880, Abcam, UK), corticosterone (AC-14F1, Xema, Russia), and serotonin (ab133053, Abcam, UK) were assayed in 2-week-old and 3-month-old control and NH-exposed rats. To assay serotonin concentration in the raphe nuclei, 3-month-old control and NH-exposed rats were decapitated, and the raphe nuclei were excised. A cytosolic fraction was then isolated via the Nuclear and Cytoplasmic Protein Extraction Kit (78833, NEPERTM Nuclear and Cytoplasmic Extraction Reagents, Thermo Scientifc, USA). Serotonin concentration in the raphe cytosolic fraction was measured using a commercial ELISA kit (ab133053, Abcam, UK), normalizing the data to the concentration of total protein, as measured via the Pierce™ Rapid Gold BCA kit (Thermo Scientifc, USA). All procedures were performed according to the manufacturers' instructions, while colorimetric measurements were accomplished using a CLARIOstar PLUS tablet reader (BMG Labtech, Germany).

Behavioral tests. The behavior of adult (3-month-old) control and NH-exposed rats was assessed in the open field and elevated plus maze tests for exploratory activity and anxiety levels, respectively. The animals were tested in the morning (starting from 10 a.m.) in a soundproof place.

The open field test (Open Science, Russia) was carried out on a circular arena (diameter 97 cm, wall height 42 cm) with the surface divided into twelve (peripheral zone) and seven (central zone) sections.

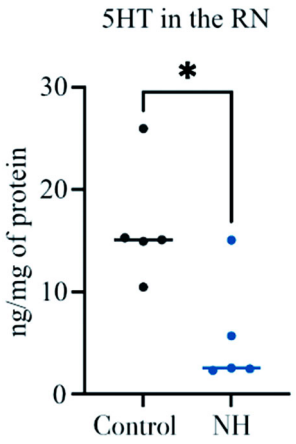

Fig. 3. Effects of neonatal hypoxia (NH) on serotonin (5HT) concentration in the raphe nuclei (RN) of 3-month-old rats ($n = 5$). * Significant differences vs. control group, $p < 0.05$ (Mann–Whitney test).

The central zone was brightly illuminated (100–120 lux). Each rat was placed in the center of the arena. A ceiling-mounted camera recorded rat movements. The total number of section-crossings in the peripheral (peripheral activity) and central (central activity) zones, the number of rearings (vertical activity) and hole explorations (exploratory activity), as well as grooming time, were measured over 5 min.

The elevated plus maze (Open Science, Russia) (120 × 120 × 40 cm, height above the floor 1 m) consisted of four elevated arms (two open and two enclosed), arranged to form a plus shape. The four arms were interconnected by a central rectangular platform (10 × 10 cm). Both the central platform and open arms were brightly illuminated (100–120 lux), while the enclosed arms were poorly lit (30 lux). Each rat was placed on the central platform with its muzzle toward the open arm. A ceiling-mounted camera recorded rat movements. The time spent in the open and enclosed arms, the time spent on the central platform (center time reflecting central activity), the number of head dips from the open arms, the number of transitions between the enclosed arms, and grooming time were measured over 5 min.

Statistics. Statistical data processing was carried out using the GraphPad Prism 10 software. The Shapiro–Wilk test ($p > 0.05$) and the quantile-quantile (QQ) plot were used to assess the normality of data distributions. The homogeneity of variances was assessed via the Fisher's exact test. The Student's *t*-test was used as a parametric one ($p < 0.05$), while in the case of sample heterogeneity, the Welch's test was used ($p < 0.05$). Data were presented as $M \pm SEM$. The Mann–Whitney *U*-test was used as a nonparametric one ($p < 0.05$), and the data were presented by box and whisker plots.

RESULTS

Effect of neonatal hypoxia on hormonal blood parameters in juvenile and adult rats

NH led to a significant decrease in plasma ACTH levels in both juvenile 2-week-old (Fig. 2a, $p = 0.018$, Welch's *t*-test) and adult 3-month-old rats (Fig. 2d, $p = 0.05$, Welch's *t*-test). Moreover, neither in 2-week-old nor in 3-month-old NH-exposed rats did the decrease in ACTH levels have an effect on corticosterone concentration (Figs. 2b, 2e). In addition, when measuring plasma serotonin concentrations, no differences were also found between control and NH-exposed juvenile and adult animals (Figs. 2c, 2f).

Effects of neonatal hypoxia on serotonin concentration in the raphe nuclei of adult rats

Serotonin concentration in the raphe nuclei of adult rats significantly decreased (Fig. 3, $p = 0.03$, Mann–Whitney test).

Effects of neonatal hypoxia on behavior of adult rats in open field and elevated plus maze tests

A comparative analysis of behavior in the open field and elevated plus maze tests revealed significant differences between control and NH-exposed rats (Figs. 4, 5).

In the open field test, NH-exposed rats demonstrated significantly decreased peripheral (Fig. 4a, $p = 0.008$, Student's *t*-test), central (Fig. 4b, $p = 0.006$, Mann–Whitney test), and vertical activity (Fig. 4c, $p = 0.05$, Student's *t*-test) compared to control animals. There were no differences in the number of hole explorations or grooming time between control and NH-exposed animals (Figs. 4d, 4e).

In the elevated plus maze test, NH-exposed rats were distinguished by a significant decrease in the time spent in the open arms (Fig. 5a, $p = 0.005$, Mann–Whitney test) and an increase in the time

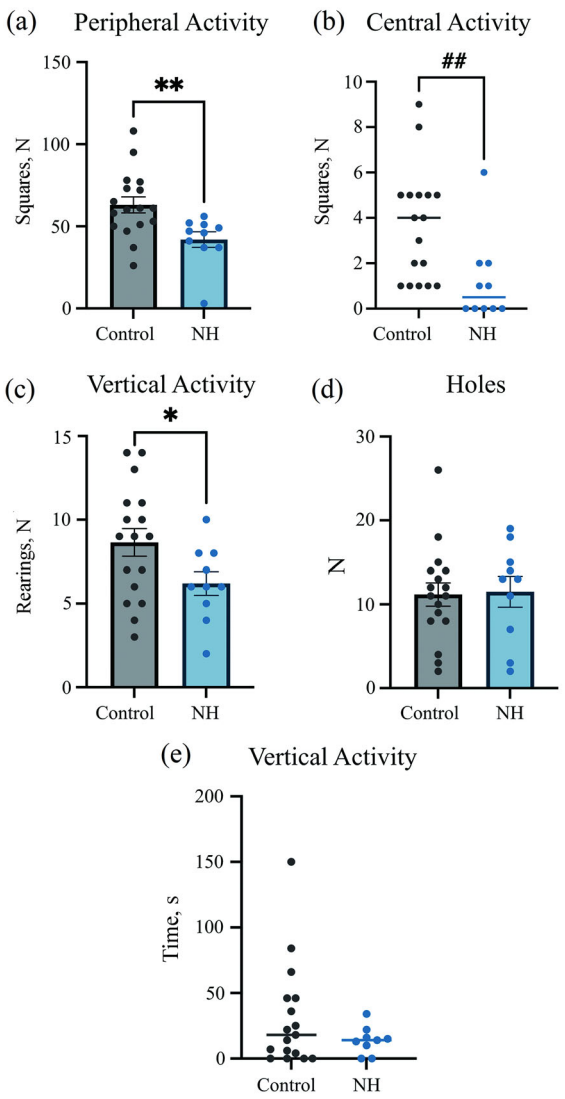

Fig. 4. Effects of neonatal hypoxia (NH) on peripheral motor activity (a), central motor activity (b), number of rearings (vertical activity) (c), number of hole explorations (d), and grooming time (e) in adult rats in the open field test (n = 10–17). Significant differences vs. control group: * $p < 0.05$ (Student's t-test); ** $p < 0.01$ (Student's t-test); ## $p < 0.01$ (Mann–Whitney test).

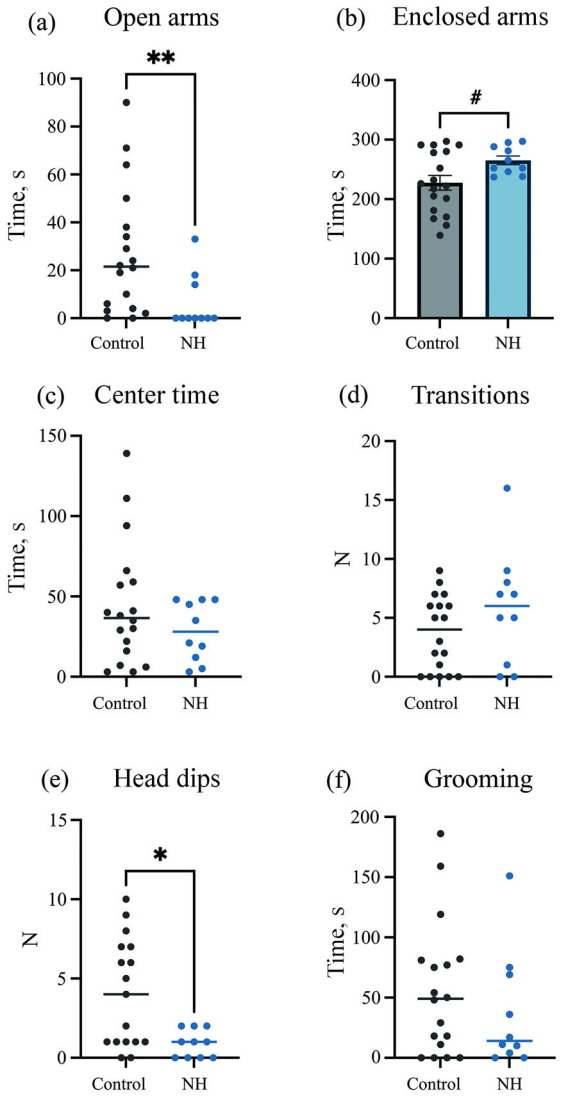

Fig. 5. Effects of neonatal hypoxia (NH) on the time spent in the open arms (a), enclosed arms (b) and central platform (c), in the number of transitions between the enclosed arms (d) and head dips from the open arms (e), and in grooming time (f) in adult rats in the elevated plus maze test (n = 10–17). Significant differences vs. control group: * $p < 0.05$ (Mann–Whitney test), ** $p < 0.01$ (Mann–Whitney test), # $p < 0.05$ (Student's t-test).

spent in the enclosed arms (Fig. 5b, $p = 0.04$, Student's t-test). In addition, NH-exposed rats exhibited fewer head dips from the open arms compared to controls (Fig. 5e, $p = 0.02$, Mann–Whitney test), but did not differ in the center time (Fig. 5c), number of transitions between the enclosed arms (Fig. 5d), and grooming time (Fig. 5f).

DISCUSSION

Hypoxia endured in the pre- and neonatal periods can lead to malformations of the central nervous system (CNS), which also entails altered behaviors that depend not only on the type and intensity of hypoxia/stress but also on the developmental period in which these alterations occur.

In this work, we investigated the behavior of adult rats exposed to hypobaric hypoxia on postnatal days 8–10 and attempted to assess the peculiarities of the serotonin system and functional disorders/modifications of the hypothalamic–pituitary–adrenocortical (HPA) axis. The open field and elevated plus maze

tests are widely used to assess anxiety and exploratory activity levels in animals in an unfamiliar setting. So, we deemed appropriate to use these tests in the present work to study the behavioral features of adult rats that had experienced hypoxia on postnatal days 8–10. As it turned out, even a moderate hypoxic exposure on these days led to altered behavior of adult rats, namely, increased anxiety level and decreased orientation–exploratory behavior. Experimental rats looked more passive compared to control animals, as manifested in their reduced motor activity at the open field periphery, decreased number of entries to the center of the field and rearings compared to controls. A similar type of behavior was shown in the work in which rats were exposed to normobaric hypoxia (7% oxygen and 93% nitrogen) in the postnatal period from day 7 to day 14, which also resulted in a decrease in motor activity and the number of rearings in adulthood [8]. In our study, similar behavioral features were also tracked in the elevated plus maze test, namely a decrease in the time spent in the open arms and an increase in that in the enclosed ones, as well as a decrease in the number of head dips from the open arms. Previously, we obtained similar results when studying the behavior of adult rats exposed to severe hypobaric hypoxia on days 14–16 of gestation [13, 14]. In these works, the disturbances in orientation–exploratory behavior and elevated level of anxiety may have been determined by changes in the functional activity of neurons, induced by a hypoxic exposure in the perinatal period, as confirmed by decreased serotonin levels in the raphe nuclei of those animals.

Hypoxia is a common neonatal stressor that leads to significant short-term distress and long-term complications [15]. Successful adaptation to neonatal hypoxia requires a coordinated physiological response, including an increase in glucocorticoid release from the adrenal cortex [16]. We hypothesized that neonatal exposure to moderate hypoxia, as well as prenatal hypoxia/stress, would result in changes in HPA axis activity in adult rats. Indeed, it has been shown that both juvenile (2-week-old) and adult (3-month-old) NH-exposed rats have significantly lower plasma ACTH levels than control animals, although coticosterone and serotonin levels are indistinguishable from control levels. The effect of perinatal hypoxia on HPA axis development is well documented. A number of studies have shown that pituitary and adrenocortical responses to hypoxia differ significantly at different stages of ontogenesis [17, 18]. For example, plasma ACTH concentration after neonatal normobaric hypoxia (8%) is significantly higher in 8-day-old than in 2-day-old rat pups, while in 5-day-old pups, ACTH level does not correlate with corticosterone concentration. The authors suggest that 5 days postpartum is a critical period during which there forms a direct dependence of adrenal glucocorticoid production on incoming ACTH [17, 18]. A key component of the response to hypoxia is the adrenomedullary production of catecholamines due to systemic (e.g., cardiovascular) and local stimulatory effects on adrenal cortex function [19–22]. The development of spinal innervation pathways of the brain matter and adrenal cortex is completed by the age of 8 days [23]. In the neonatal period, adrenomedullary chromaffin cells possess a mechanism to activate the synthesis and release of catecholamines in response to decreased oxygen supply [24]. Meanwhile, after 8 days of postnatal ontogenesis in rats, this mechanism stops functioning any longer [25]. In this model, elevated ACTH levels on day 8 postpartum regulate basal corticosterone levels and maintain HPA axis activity.

In our experiments, we applied hypoxia (360 mm Hg, 10% O_2, 3×2 h with a 24-h inter-session interval) and determined ACTH levels 4 days after the last hypoxic/stress session (i.e. on day 14 postpartum) and in adult males. The observed stable NH-induced decrease in ACTH levels may probably represent the outcome of HPA axis reprogramming aimed at further maintaining normal corticosterone levels in these animals throughout their life. In turn, anxiety-like behavior in rats in a model of prenatal hypoxia was due to maternal stress during pregnancy, which diminished the efficacy of glucocorticoid negative feedback through decreased expression of extrahypothalamic glucocorticoid receptors in the offspring brain throughout life [14, 26]. Thus, hypoxic exposure during pre- and postnatal ontogenesis leads to changes in the level of anxiety due to various modifications of the glucocorticoid system.

In our previous studies, it was shown that serotonin levels in the raphe nuclei of adult rats exposed to severe hypoxic exposure on prenatal days 14–16 did not differ from the control level [26]. However, in the NH model, it was found that although plasma serotonin levels in experimental animals do not dif-

fer from those in the control, the raphe serotonin content in adult NH-exposed rats is significantly lower than in control animals. The current consensus opinion on the role of biogenic amines in the pathophysiology of psychological disorders attributes depression, mania, and anxiety disorders to decreased serotonin levels in the CNS [27, 28]. The reduced serotonin level accounts for the manifestations of depressed emotional state in these animals.

Thus, neonatal hypoxia in rats at the age of 8–10 days causes significant alterations in the activity of the HPA axis and serotonin system, as echoed in decreased exploratory behavior and increased anxiety in adulthood.

AUTHORS' CONTRIBUTION

Conceptualization and study design (E.I.T.), data collection (V.A.S., O.V.V.), data processing (V.A.S., O.V.V.), writing and editing the manuscript (E.I.T., V.A.S., O.V.V.).

FUNDING

This work was supported by ongoing federal budget funding to Pavlov Institute of Physiology (no. 1023032400236-8-3.1.4). No additional grants to carry out or supervise this particular research were obtained.

ETHICS APPROVAL

Animal-related experiments were carried out in compliance with the NIH Guidelines for the care and use of laboratory animals (http://oacu.od.nih.gov/regs/index.htm) and requirements of the Council Directive 86/606/EEC on the use of animals for experimental research. The experimental protocol was approved by the local Ethics Committee of the Pavlov Institute of Physiology (Minutes no. 08/02 of 02.08.2022).

CONFLICT OF INTEREST

The authors of this work declare that they have no conflict of interest.

REFERENCES

1. Beversdorf DQ, Stevens HE, Jones KL (2018) Prenatal Stress, Maternal Immune Dysregulation, and Their Association with Autism Spectrum Disorders. Curr Psychiatry Rep 20(9): 76. https://doi.org/10.1007/s11920-018-0945-4
2. Rocha-Ferreira E, Hristova M (2016) Plasticity in the Neonatal Brain following Hypoxic-Ischaemic Injury. Neural Plast 2016: 4901014. https://doi.org/10.1155/2016/4901014
3. Bennet L, Tan S, Van den Heuij L, Derrick M, Groenendaal F, van Bel F, Juul S, Back SA, Northington F, Robertson NJ, Mallard C, Gunn AJ (2012) Cell therapy for neonatal hypoxia-ischemia and cerebral palsy. Ann Neurol 71: 589–600. https://doi.org/10.1002/ana.22670
4. Rice JE 3rd, Vannucci RC, Brierley JB (1981) The influence of immaturity on hypoxic-ischemic brain damage in the rat. Ann Neurol 9: 131–141. https://doi.org/10.1002/ana.410090206
5. Yager JY, Ashwal S (2009) Animal models of perinatal hypoxic-ischemic brain damage. Pediatr Neurol 40: 156–167. https://doi.org/10.1016/j.pediatrneurol.2008.10.025
6. Arteni NS, Salgueiro J, Torres I, Achaval M, Nett CA (2003) Neonatal cerebral hypoxia-ischemia causes lateralized memory impairments in the adult rat. Brain Res 973: 171–178. https://doi.org/10.1016/s0006-8993(03)02436-3
7. Millar LJ, Shi L, Hoerder-Suabedissen A, Molnár Z (2017) Neonatal Hypoxia Ischaemia: Mechanisms, Models, and Therapeutic Challenges. Front Cell Neurosci 11: 78. https://doi.org/10.3389/fncel.2017.00078
8. Bakhtazad S, Ghotbeddin Z, Tabandeh MR, Rahimi K (2024) Alpha-pinene ameliorate behavioral deficit induced by early postnatal hypoxia in the rat: study the inflammatory mechanism. Sci Rep 14(1): 6416. https://doi.org/10.1038/s41598-024-56756-1.
9. Hermansen CL, Lorah KN (2007) Respiratory distress in the newborn. Am Fam Physician 76: 987–994.
10. Trnski S, Nikolić B, Ilic K, Drlje M, Bobic-Rasonja M, Darmopil S, Petanjek Z, Hranilovic D, Jovanov-Milosevic N (2022) The signature of moderate perinatal hypoxia on cortical organization and behavior: altered PNN-Parvalbumin interneuron connectivity of the cingulate circuitries. Front Cell Dev Biol 10: 810980. https://doi.org/10.3389/fcell.2022.810980
11. Nikolic B, Trnski-Levak S, Kosic K, Drlje M, Banovac I, Hranilovic D, Jovanov-Milosevic N (2024) Lasting mesothalamic dopamine imbalance and altered exploratory behavior in rats after a mild neonatal hypoxic event. Front Integr Neurosci 17: 1304338.

https://doi.org/10.389/fnint.2023.1304338
12. Vetrovoy OV, Stratilov VA, Lomert EV, Tyulkova EI (2022) Possible correction of impairments to the glucocorticoid system of the rat hippocampus induced by prenatal hypoxia. Neurochem J 16(3): 228–232. (In Russ). https://doi.org/10.1134/S1819712422030126
13. Stratilov VA, Vetrovoy OV, Vataeva LA, Tyulkova EI (2022) Age-Associated Changes in Exploratory Activity in the Open Field Test in Rats Surviving Prenatal Hypoxia. Neurosci Behav Physiol 52(2): 271–276. (In Russ). https://doi.org/10.31857/S0044467721030102
14. Stratilov V, Potapova S, Safarova D, Tyulkova E, Vetrovoy O (2024) Prenatal Hypoxia Triggers a Glucocorticoid-Associated Depressive-like Phenotype in Adult Rats, Accompanied by Reduced Anxiety in Response to Stress Int J Mol Sci 25: 5902. https://doi.org/10.3390/ijms25115902
15. Raff H, Jacobson L (2007) Glucocorticoid feedback control of corticotropin in the hypoxic neonatal rat. J Endocrinol 192(2): 453–458. https://doi.org/10.1677/JOE-06-0103
16. Hanukoglu A, Fried D, Nakash I, Hanukoglu I (1995) Selective increases in adrenal steroidogenic capacity during acute respiratory disease in infants. Europ J Endocrinol 133: 552–556. https://doi.org/10.1530/eje.0.1330552
17. Bruder ED, Taylor JK, Kamer KJ, Raff H (2008) Development of the ACTH and corticosterone response to acute hypoxia in the neonatal rat. Am J Physiol Regul Integr Comp Physiol 295: R1195–R1203. https://doi.org/10.1152/ajpregu.90400.2008
18. Chintamaneni K, Bruder ED, Raff H (2013) Effects of age on ACTH, corticosterone, glucose, insulin, and mRNA levels during intermittent hypoxia in the neonatal rat. Am J Physiol Regul Integr Comp Physiol 304: R782–R789. https://doi.org/10.1152/ajpregu.00073.2013
19. Bodnar M, Sarrieau A, Deschepper CF, Walker CD (1997) Adrenal vasoactive intestinal peptide participates in neonatal corticosteroid production in the rat. Am J Physiol Regul Integr Comp Physiol 273: R1163–R1172. https://doi.org/10.1152/ajpregu.1997.273.3.R1163
20. Ehrhart-Bornstein M, Bornstein SR, Gonzalez-Hernandez J, Holst JJ, Waterman MR, Scherbaum WA (1995) Sympathoadrenal regulation of adrenocortical steroidogenesis. Endocr Res 21: 13–24. https://doi.org/10.3109/07435809509030417
21. Schinner S, Bornstein SR (2005) Cortical-chromaffin cell interactions in the adrenal gland. Endocr Pathol 16: 91–98. https://doi.org/10.1385/ep:16:2:091
22. Seidler FJ, Slotkin TA (1985) Adrenomedullary function in the neonatal rat: responses to acute hypoxia. J Physiol 358: 1–16. https://doi.org/10.1113/jphysiol.1985.sp015536
23. Engeland WC (1998) Functional innervation of the adrenal cortex by the splanchnic nerve. Horm Metab Res 30: 311–314. https://doi.org/10.1055/s-2007-978890
24. Nurse CA, Buttigieg J, Thompson R, Zhang M, Cutz E (2006) Oxygen sensing in neuroepithelial and adrenal chromaffin cells. Novartis Found Symp 272: 106–114.
25. Tin W (2004) Optimal oxygen saturation for preterm babies. Do we really know? Biol Neonate 85: 319–325. https://doi.org/10.1159/000078173
26. Vetrovoy O, Stratilov V, Lomert E, Tyulkova E (2023) Prenatal Hypoxia-Induced Adverse Reaction to Mild Stress is Associated with Depressive-Like Changes in the Glucocorticoid System of Rats. Neurochem Res 48: 1455–1467. https://doi.org/10.1007/s11064-022-03837-0
27. Kandel E (2001) Depression, mania and anxiety disorders. In: Kandel E, Schwartz J, Jessell T (Eds) Principles of Neural Science; 4th edn. McGraw-Hill, New York, pp. 1209–1225.
28. Mitroshina EV, Marasanova EA, Vedunova MV (2023) Functional Dimerization of Serotonin Receptors: Role in Health and Depressive Disorders. Int J Mol Sci 24(22): 16416. https://doi.org/10.3390/ijms2422

Translated by A. Polyanovsky