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Perinatal Stressors as a Factor in Impairments to Nervous System Development and Functions: Review of In Vivo Models

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The human body is faced with stress throughout ontogeny. At the stage of intrauterine development, the mother's body serves as a source of resources and most of the humoral factors supporting the development of the fetus. In normal conditions, maternal stress-related humoral signals (e.g., cortisol) regulate fetal development; however, distress (excessive pathological stress) in the perinatal period leads to serious and sometimes irreversible changes in the developing brain. The mother being in an unfavorable psychoemotional state, toxins and teratogens, environmental conditions, and severe infectious diseases are the most common risk factors for the development of perinatal nervous system pathology in the modern world. In this regard, the challenge of modeling situations in which prenatal or early postnatal stresses lead to serious impairments to brain development and functioning is extremely relevant. This review addresses the various models of perinatal pathology used in our studies (hypoxia, exposure to valproate, hyperserotoninemia, alcoholization), and assesses the commonality of the mechanisms of the resulting disorders and behavioral phenotypes forming in these models, as well as their relationship with models of perinatal pathology based on the impact of psychoemotional stressors.

Keywords: intrauterine development, perinatal pathology, perinatal stress, animal models, valproic acid, perinatal hypoxia, perinatal alcoholization, hyperserotoninemia.

Perinatally-Induced Pathologies of Human CNS Development. During intrauterine and early postnatal development, the central nervous system (CNS) is extremely sensitive to the influences of a wide range of factors: from the physiological parameters of the mother's body to external physicochemical influences encountered by the mother, the fetus, and the neonate. Perinatal distress is most commonly associated with a negative psychoemotional state and impairment to the mother's physical wellbeing during pregnancy and childbirth, the various types of traumatic experience she has endured, and impairments to the parent-child interaction (for example, in the case of maternal depression) [Dubynin et al., 2014].

In addition, the list of factors forming conditions for the development of distress in offspring includes the obligate intake of medications for the treatment of persistent pathological conditions in the mother (antidepressants, anticonvulsants), taking compounds with narcotic properties (with concomitant intoxication and the development of withdrawal symptoms), an environment with unfavorable ecological properties, and infectious processes occurring in the mother's body (accompanied by high proinflammatory cytokine concentrations). All the above are risk factors for the formation of disorders of the development and functioning of the CNS, which can be apparent both immediately (in early childhood) or delayed to a later age [Elefant et al., 2020; Cook et al., 2020; Boucoiran et al., 2020; Gagnon-Chauvin et al., 2020; Guedeney and Dupong, 2020; Kaseka et al., 2020].

The consequences of perinatal stress are extremely diverse. Among them are both extremely severe symptoms and conditions (major motor and sensory impairments, focal epilepsy, and even cerebral edema that can lead to neo-

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natal death), and conditions affecting almost exclusively the psychoemotional and cognitive spheres, i.e., various types of autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD), and dyslexia.

In general, these impairments produce a heavy socio-economic burden that is borne by patients' families, social care structures, and the state as a whole; the costs of care, rehabilitation, and education of children with early developmental disorders are growing year by year, and sometimes the severity of a perinatal pathology is so great that the person needs support and corrective therapy throughout life.

The most widely held view is that the peculiar sensitivity of the CNS to stress factors during the perinatal period is due to the increased plasticity of developing neural networks at certain stages of brain development. These stages are referred to as "windows" – critical periods (CP) during which the nervous system is particularly susceptible to the effects (not only negative, but also positive) of various influences. For example, immediately after birth, the infant's brain is extremely sensitive to sensory information (primarily visual, sound, tactile) coming from the environment. Sensory input is important for the normal development of the auditory and visual systems, and when it is deficient (or, conversely, when there is excessive abnormal activation of the corresponding inputs), there may be failures in the formation of neural contacts, problems with the development of new skills at subsequent stages of ontogeny, and, in particular, disorders of speech development.

On the other hand, the increased sensitivity of neural networks during the critical periods of their maturation provides prospects for targeted therapeutic interventions – psychological, pedagogical, pharmacological, and even surgical. Returning to the example of sensory systems, early implantation of hearing implants in patients with complete or partial hearing loss (lesions to the cochlear apparatus) and restoration of vision (after removal of cataracts in infants, a fairly common congenital pathology) is most successful when the corrective procedures are carried out in early childhood (in the case of the auditory system – before age two years). With later surgery, it is much more difficult for patients to develop normal speech and visual skills [Cisneros-Franco et al., 2020].

An important factor in perinatal stress that affects the further development of the child's brain is the process of childbirth. Birth traumas, particularly neonatal hypoxia, not only cause severe pathologies such as cerebral palsy and epilepsy, but also provoke less marked delayed neurophysiological and behavioral disorders. Among children with ADHD, as well as those with various forms of ASD, the percentage experiencing difficult childbirth, premature birth, or resuscitation is much higher than among the essentially healthy population without marked signs of social or cognitive impairment and no reduction in the rate of psychoemotional development. Children who have experienced perinatal hypoxia are characterized by impaired motor functions, reduced learning ability, inattention, hyperactivity, and increased anxiety [Piesova and Mach, 2020; Smith et al., 2014]. Morozova and Morozov [2008] noted that the consequences of perinatal pathology can persist until adolescence, hampering learning and social integration. Similar data on the manifestations and dynamics of the symptoms of ADHD, ASD, and other disorders are also given in a number of non-Russian studies.

Thus, several studies have shown that stress-mediated reprogramming of the hypothalamic-pituitary-adrenal axis in the pre- and early postnatal period in humans plays a key role in the formation primarily of anxiety disorders [Welberg and Seckl, 2009; Weinstock, 2009; Juruena et al., 2020]; perinatal stress is a risk factor for the formation of the most common psychiatric disorders: depressive disorders, bipolar disorder, schizophrenia, and autism spectrum disorders [Kinney, 2008; Markham and Koeing, 2012].

Analysis of the pathologies of early development often notes the presence of genetic anomalies which become apparent under the influence of environmental factors operating as triggers for the formation of particular behavioral phenotypes [Chaste and Leboyer, 2012]. Hormonal disorders in the mother's body, atmospheric pollution, heavy metals, many xenobiotics (such as phthalates) that enter the woman's body with food during pregnancy can cause genetic and epigenetic changes in the fetus, seriously increasing the risk of pathological changes. In this regard, many researchers refer not only to a genetic predisposition, but also to the interaction between heredity and environment; the concept of this interaction is most widely used in relation to risk factors for the development of autism spectrum disorders [Cheroni et al., 2020].

It should be noted that the sequelae of perinatal stresses are fixed in long-term ontogeny and persist until puberty, particularly as a result of epigenetic modification of genes associated with stress regulation [Sosnowsky et al., 2018].

The use of specialized psychological and pedagogical practices (for example, Applied Behavior Analysis (ABA) therapy) and medical (pharmacological) methods produce beneficial effects in many patients with perinatally-induced psychoemotional and social disorders [Donaldson et al., 2020]. However, early brain development is so important for the further formation of behavior and general psychophysiological status that, as adults, these people often continue to experience difficulties in socialization and carrying out certain cognitive tasks and are at elevated risk of mental disorders, the most common of which are increased anxiety and depressive states [Liu et al., 2020].

General Approaches to Modeling Perinatally-Induced CNS Pathologies in Laboratory Animals. Pharmacological and physicochemical in vivo modeling (primarily in rodents) of stress-inducing perinatal actions and analysis of the mechanisms and consequences of the resulting disorders and the developmental dynamics of responses can improve the diagnosis, correction and treatment of the corresponding

conditions in humans. It is important to take account of the fact that the effects observed in in vivo models cannot be interpreted as a complete reproduction of specific pathologies in humans. We also note the comorbidity of many neurochemical, neurophysiological, and behavioral disorders at early ages, which complicates the processes of both interpreting experimental data and making clinical diagnoses [Morozov, 2018]. For example, in the case of laboratory animals, we can generally refer only to complex changes in behavior, such as delayed locomotor development, decreased exploratory activity, and elevated anxiety as compared with control groups, as well as deterioration in many types of social interaction (social preference, maternal care, reactions during play), and impairment of the ability to perform learning and memory formation tasks.

The classification of the models regarded below is based primarily on the method used for induction of perinatal pathology; the results obtained sometimes have a significant degree of similarity, indicating a high level of non-specificity of the stress-inducing factors under investigation and their generalized effects. To be specific, the models presented below use hypoxia, two approaches based on administration of pharmacological drugs (valproate and SSRIs), and a model of alcoholism. In the final part, we will compare these protocols with some of the "classic" approaches to creating perinatal stress.

The generally accepted view is that the most important critical periods of sensitivity of nervous system formation in rodents to physicochemical influences are displaced in time relative to human development into the postnatal period. In rats and mice, in contrast to *Homo sapiens*, many of the most important stages of brain development occur postnatally [Schaeffer et al., 2013]. Some authors have provided more detailed comparisons of pre- and postnatal ontogeny of rodents and humans. Gelashvili [2008] noted that the human embryonic development phase corresponds approximately to seven days of development in rats and the placental phase to the next 10, while the last four days of rat prenatal development correspond to the late fetal stages of human development; one day of life in the early postnatal development of a rat is approximately comparable to 52 days of life for a neonate.

According to the histological and anatomical data obtained by Rice and Barone [2000], prenatal development in rats corresponds to about 19 weeks of human intrauterine development, while the early neonatal period (days 1–19 of life in rats) corresponds to weeks 19–40 of human intrauterine development (the last trimester of fetal development). A similar comparison of developmental periods in rats and humans was provided by [Karpova et al., 2009; Thompson et al., 2009]. Comparison of the rates of brain development and analysis of the histological and functional ontogeny of its various regions and specific neuronal systems made it possible to correlate the brain of a rat pup during the second week of postnatal development with the brain of a full-term neonate and the brain of a neonatal rat in the first week with the nervous system of a premature baby [Lai, Yang, 2011]. However, it may be more correct to compare ontogeny for individual CNS mediator systems or structures within the framework of different areas of research.

Models of Perinatal Hypoxia. Perinatal hypoxia plays an important role among the factors having adverse stress-inducing effects on central nervous system development [Golosnaya et al., 2004; Hossain, 2008]. Animal experiments have shown that transient hypoxia in late pregnancy affects neuron migration in the brain. Neonatal hypoxia causes a number of anatomical changes and cognitive impairments in rodents, such as decreased brain volume, ventricular dilation, delayed development of sensory and motor reflexes, hyperactivity, impaired spatial learning, as well as neuronal damage, impaired axon myelination and sprouting, and changes in the contents of neurotrophic factors, monoamines, etc. [Dubrovskaya et al., 2002; Wang et al., 2013; Ujhazy et al., 2013]. Prenatal hypoxia leads to disruption of synaptic processes associated with the formation of both long-term and short-term memory, along with impairment to the sensory, motor, and cognitive functions of the brain [Dubrovskaya, 2007; Lee et al., 2021]. There is a relationship between the consequences of prenatal hypoxia and exposure time: hypoxic stress applied at different stages of embryogenesis affects the formation of the nervous system in different ways [Vasiliev, 2007].

Early postnatal hypoxia also has a wide range of adverse effects on the "maturing" rat CNS. Even a single episode of normobaric hypoxia on day 2 of life in rats leads to increases in mortality and long-term changes in general physical and early locomotor development [Sukhanova et al., 2018]. Animals subjected to hypoxia have slowed weight gain, elevated anxiety levels, impaired learning, and altered BDNF levels in the hypothalamus (at age one month) and hippocampus (at age two months) [Sukhanova et al., 2018]. Comparison of the sequelae of hypoxic exposure documented in animal experiments with clinical study results from premature infants experiencing hypoxia indicates the appropriateness of this model [Sukhanova et al., 2015; Sukhanova et al., 2018]. Similar results have recently been obtained using C57BL/6 mice [Khuhareva et al., 2021a, 2021b].

Exposure to Pharmacological Agents: Valproates. A significant number of pharmacological agents used in the clinic are characterized by embryotoxicity and probable teratogenic effects. However, there are situations where the intake of such compounds is vital to maintain the well-being of the mother's body and maintain pregnancy.

The long clinical history of the use of various drugs in successive stages of pregnancy has made it possible to identify pharmacological agents that have the most significant adverse impacts on developing offspring. These substances (generally at high and ultra-high doses) then entered use for modeling perinatal pathology in rodents. In the most widely

used approach, experimental animals (pregnant females or neonates) are injected with antiepileptic drug sodium valproate or valproic acid itself (VPA), which block GABA transferase and histone deacetylase. Also, data have been obtained on the adverse effects of antidepressants of the selective serotonin reuptake inhibitor (SSRI) group and other compounds affecting the activity of the serotonergic system of the brain in the developing fetus.

In the clinic, "fetal valproate syndrome" – a set of teratogenic changes occurring in a child under the influence of VPA and its derivatives – has been known since the second half of the 20th century. A number of serious fetal disorders have been identified, such as spina bifida, trigonocephaly, epicanthus, medial eyebrow deficiency, broad nasal root, and long lower lip [Kulkarni et al., 2006]. Exposure of embryos to VPA also causes neural tube defects. Metabolic complications are known to occur [Branten et al., 1998], along with valproate-induced encephalopathies and complex psychoemotional problems (depressive-like state, hyperactivity, severe disturbances to sleep/waking rhythms).

VPA later found use in in vivo models in rodents. Acute prenatal high-dose VPA (single injections to female rats on the day 13 of pregnancy; 600 mg/kg) is the most widely used model and comes with significant mortality, smaller litters, and sometimes obvious physical defects in offspring. Models based on chronic (1–2 weeks) postnatal administration of the same agent appeared somewhat later. Postnatal valproate models do not result in pup deaths; behavioral changes are no less pronounced than in the prenatal variant of administration of VPA and its salts [Gedzun et al., 2019; Dobrovolskiy et al., 2020].

In general, valproate models are characterized by slowing of development in the motor domain (later formation of vestibular reflexes and components of locomotor programs), decreased orientational/exploratory activity, and increased anxiety. Disturbances to social behavior are also observed, expressed both as early changes in the parameters of the mother/pup interaction and in indicators of social preference (decreased desire for "social novelty"), and in delayed impairments to parental behavior in females – which provided an additional model of maternal depression (postpartum depression, PPD) [Dubynin et al., 2014].

The set of pathological changes observed in experimental animals at different stages of development is interpreted by many researchers as a model of an ASD-like state (mainly due to a diversity of impairments to social interactions). The similarity of VPA-induced models with clinical cases of autistic disorders has been demonstrated not only at the behavioral, but also at the histological and molecular genetic levels [Dobrovolskiy et al., 2020; Gedzun et al., 2019].

Hyperserotoninemia. Data on SSRI as a risk factor for the development of early disorders are currently very contradictory. With this in mind, many research groups are studying the effects on the CNS and behavior under different protocols for administration of SSRIs to experimental animals. Chronic postnatal exposure to fluvoxamine from day 1 to day 14 of life has been shown to produce complex behavioral disorders, including delayed physical and locomotor development and changes in biogenic amine contents in the nervous system of mouse offspring [Bond et al., 2020]. Prenatal fluvoxamine has also ben found to cause long-term disturbances in social behavior and sensorimotor reactions in experimental animals. Other pharmacological agents are also used to induce perinatally stressful hyperserotoninemia: serotonin itself, 5-hydroxytryptophan (5-HTP, a serotonin precursor), and monoamine oxidase inhibitors (MAO) – both selective for MAO-A and non-selective (for example, tranylcypromine) [Blazevic et al., 2012]. In addition, ligands of certain serotonin receptor types and subtypes are used, sch as 5-methoxytryptamine (5MT, a 5-HT1/5-HT2 agonist) [Cannizaro et al., 2008].

At the biochemical level, studies in "serotonin" models demonstrated a generalized long-term disturbance in the content of biogenic amines in the CNS of experimental animals, which can be interpreted as an antidepressant "withdrawal syndrome" formed in the perinatal period [Glazova et al., 2014]. Due to the wide range of targets of serotonin and the diversity of the functions of the 5-HT system, it is extremely difficult to single out the leading role of any particular physiological process in hyperserotoninemia. Along with changes in the functioning of the brain monoaminergic systems, defects in neurogenesis and synapse formation (the overall "connectivity" of the CNS) which are regulated by serotonin from the early prenatal period, are most widely discussed.

Phenotypic (behavioral) manifestations in serotonin models sometimes go in different directions: hyper- or hypolocomotion, increased or decreased pain sensitivity, etc. Thus, behavioral disturbances in studies in a model of perinatal exposure to 5-methoxytryptamine include reduced risk behavior and the absence of "despair behavior" in the forced swim test [Cannizaro et al., 2008]. In general, early hyperserotoninemia significantly increases stress reactivity and alters the cognitive plasticity of test animals [Blazevic et al., 2012]. The overall patterns of behavioral disturbances in the perinatal modulation of the serotonin system partially coincide with those described for the VPA models. The similarity is most marked in the domain of impaired social reactions in animals exposed to SSRI in the perinatal period [Bond et al., 2020].

Perinatal Alcoholization. Narcotics occupy a special place among pharmacologically induced models of perinatal pathology [Cook, 2020]. Despite strict prohibition and contraindications during pregnancy, they cause developmental disorders in the body and nervous system of neonates around the world. Sequalae of using nicotine, cannabinoids, and opioid drugs have been described. The leading place (in terms of socio-economic and socio-demographic significance) in this series is occupied by alcohol.

Children exposed to ethanol in utero develop fetal alcohol syndrome (FAS), a characteristic set of develop-

mental disorders. This includes changes in the proportions of the head; in addition, ADHD, deterioration in cognitive abilities, a tendency to form pharmacological and behavioral addictions (primarily alcohol addiction), social disorders, excessive anxiety, and depressive-like manifestations are diagnosed [Razumkina et al., 2018; Cook, 2020]. The leading role in the formation of the behavioral phenotype of FAS (including compulsions and a high risk of addiction) is often assigned to dysregulation of the mesolimbic dopamine system of the brain [Anokhin et al., 2019]. Animal models of FAS, as well as clinical assessment of the effects of prenatal ethanol exposure, have identified D2 receptor dysfunctions, impaired neuronal DNA methylation, reduced cerebral gray matter volumes, brain blood vessel pathologies, and impairments to neuronal migration and differentiation [Cook, 2020].

Other Chemically and Physically Induced Models of Perinatal Pathology. The number of xenobiotics and physical factors that can adversely affect the developing fetal organism is clearly not limited to the chemical compounds identified above and perinatal hypoxia. A number of substances encountered by millions of people in everyday life have teratogenic effects. For example, bisphenol-A (BPA), a component of many plastics, can adversely impact development due to the estrogen-like action of some of its isomers [Song et al., 2014]. Furthermore, prenatal exposure to BPA may be a risk factor for the development of autism-like disorders, which has been confirmed both at the molecular level (impaired expression of various of the genes which have been shown to be associated with autism disorders [Thongkorn et al., 2019]), and at the behavioral level in animals exposed to BPA (cognitive impairments have been identified in experimental animals [Kundakovic et al., 2014]).

Another group of teratogenic compounds which have been investigated includes pesticides that can induce pathological processes in the developing fetal body. The pesticide chlorpyrifos is one of the best studied pesticides in terms of the spectrum of pathological effects on the developing organism. In vivo models of early developmental exposure to this pesticide are also regarded by some researchers as a model for autism-like disorders [De Felis et al., 2016; Perez-Fernandez et al., 2020].

One of the most popular and best studied of the in vivo rodent models providing direct analogies with human perinatal pathological conditions is the hyperhomocysteinemia model (induced by administration of various doses of homocysteine during perinatal development in experimental rodents). In humans, excess homocysteine often results from genetic disorders of enzyme systems, insufficiency of B vitamins in the mother's diet, or other metabolic disorders. The consequences of excess homocysteine during perinatal development include both direct disturbances to the normal course of pregnancy (termination of pregnancy, preeclampsia, etc.) and neonatal pathologies: low birth weight, impaired neural tube formation, and neurological disorders in neonates [Milyutina et al., 2016; Harutyunyan et al., 2021]. Homocysteine metabolism is similar in rodents and humans and excessive administration of homocysteine to rats in the perinatal period leads to the induction of motor development disorders and signs of anxiety, which can be corrected by the administration of B group vitamins [Yakovleva et al., 2019].

In vivo studies indicate that the leading role in the pathogenesis of the symptoms of hyperhomocysteinemia can be attributed to activation of proinflammatory cytokines and excessive production of reactive oxygen species on the background of an underdeveloped antioxidant system in the developing body [Milyutina et al., 2016; Arutyunyan et al., 2021]. In the case of BPA and chlorpyrifos, oxidative stress is also among the critical damaging factors affecting the developing fetus and causing generalized developmental disorders not only in the CNS, but also in all organ systems [Song et al., 2014; De Felis et al., 2016].

Similarity of Models and Generality of Mechanisms of Development of Stress-Induced Effects. Despite the different ways of modeling perinatal pathology, the behavioral changes observed have a high degree of similarity (both between models and on comparison of animal experimental studies with real clinical data).

The similarity is most easily observed at the behavioral level: disorders of early development, delays in motor reflex formation and locomotor and exploratory activity are the most widely recorded in experimental animals [Glazova et al., 2014; Gedzun et al., 2019; Yakovleva et al., 2019; Bond et al., 2020; Sukhanova et al., 2018]. Social reactions are clearly altered at different stages of ontogeny: early mother-dependent behavior (infant-mother attachment; age 1–2 weeks) [Dubynin et al., 2014], preference for "social novelty" (when choosing between a mother and an unfamiliar female; when choosing between a sibling and an offspring from another brood; age 4–5 weeks) [Dobrovolskiy et al., 2020; Khukhareva et al., 2020], and during play interaction (higher levels of aggressiveness; age 5–7 weeks) [Dobrovolskiy et al., 2020]. Cognitive impairments affecting the formation of long-term memory in different types of learning have been identified [Kundakovic et al., 2014; Sukhanova et al., 2014; 2019].

It is important that experimental animals show increases in levels of anxiety and depression-like signs (in the elevated plus maze, forced swim, and other tests) [Cannizaro et al., 2008; Malyshev et al., 2015; Blazevic et al., 2012; Dobrovolskiy et al., 2020]. Perinatal stress associated with exposure to hypoxia or pharmacological factors harming females (neonates) leads to disruption in the functioning of systems that provide resistance to current (situational) stress in young and even adult animals. Testing of rodents is generally continued to age 3–4 months and gradual decreases in the severity of disorders is often not recorded [Dobrovolskiy et al., 2020; Sukhanova et al., 2016]. This, in

turn, may also be a consequence of epigenetic modifications that have been demonstrated to occur in some of the models discussed above, i.e.,, valproate models [Choi et al., 2016], hypoxia models [Cristancho and Marsh, 2020], BPA models [Kundakovic et al., 2014], and models of prenatal alcohol intoxication [Bestry et al., 2022].

Despite the well-studied differences in the mechanisms of pathogenesis in the models studied, several generalized processes common to all the situations listed above can be identified:

– impaired neuron migration and synaptogenesis (degradation of both new synapse formation and synaptic pruning);

– imbalance of neurotransmitter influences in the CNS, more often shifted towards excessive excitation due to hypofunction of the GABAergic system [Marotta et al., 2020];

– neuroinflammatory processes and accompanying increases in the concentration of reactive oxygen species (work in this area has currently intensified due to the possible impact of severe COVID infection during pregnancy on the development of the fetal nervous system [Vargas, 2005; Lee, 2017; Amaral et al., 2020]).

The outcome is that changes occurring at both the cellular level (white matter, myelination, glial activation) and the level of large-scale brain structures (for example, the prefrontal cortex and its connections with other areas of the central nervous system – the nucleus accumbens, amygdala, cingulate gyrus, parietal-temporal region) are quite similar [Whittle et al., 2016; Kohls et al., 2018; Supekar et al., 2018].

The sequelae listed above are also characteristic of more "classical" methods of inducing perinatal stress (see below). Study results allow parallels to be drawn between the molecular mechanisms of perinatal stress and other types of perinatal pathologies studied in the models discussed.

In addition to being a natural selective barrier to infectious agents, maternal antibodies, and humoral factors, the placenta is also able to partially compensate for the pathological effects of distress on the fetus. For example, prenatal exposure to stress within the mother's body produces excessive activation of the hypothalamic-pituitary-adrenal axis (HPA axis), with elevated cortisol levels (in humans; corticosterone predominates in rats and mice), which has adverse affects on the developing fetus. Glucocorticoids normally play an important role in the formation of the fetus (especially the brain and lungs), and the placenta is able to regulate the glucocorticoid supply to the embryo by means of the enzyme 11-β-hydroxysteroid dehydrogenase subtype 2 (11-β-HSD2). However, excess quantities of stress-related hormones lead to a series of irreversible changes in the developing nervous system, despite the protective effects of the placenta [Charil et al., 2010; Saeki et al., 2021]. In addition to compensatory processes associated with excessive quantities of stress-activated hormones, the placenta is also able to compensate for the consequences of hypoxia [Colson et al., 2021].

These are just a few examples illustrating the potential for protecting the fetus from prenatal stress-induced pathology. Modulation of these processes is a target for the development of drugs able to minimize the effects of perinatal stress.

Comparison with Models of Perinatal Pathology Based on the Influences of Psychoemotional Stress. In this review, "classic models" of perinatal stress are taken to be minimally invasive models based on the formation of an environment uncomfortable for a pregnant female or neonates: proximity to an aggressive conspecific or a predator (the odor of a predator), movement restriction, excessive sound and/or light stimuli, and changes in keeping temperature [Weinstock et al., 2017; Crombie et al., 2021]. These models use production of moderate distress essentially not causing direct physical harm to the mother's body and in our view resembling the real-world distress situations that women find themselves in during pregnancy.

Psychoemotional and physical stress in the perinatal period correlates with significant increases in peripheral corticosterone, as well as corticotropin-releasing hormone in the offspring (as compared with control animals). In addition, perinatal stress is associated with changes in the proinflammatory cytokine expression profile in the nervous system, which also indicates similarity with the models discussed above. However, the available data are very contradictory (in relation, for example, to specific interleukins) due to variations in the experimental methods used [Angelidou et al., 2012; Creutzberg et al., 2021].

Neuroinflammation is directly related to oxidative stress and neuron death. For "classical" animal models, a relationship has been shown, for example, between maternal stress and an increased content of reactive oxygen species [Scott et al., 2020]. Clinical studies have revealed a correlation between increased levels of markers of oxidative stress and the subsequent development of signs of autistic pathology in children [Angelidou et al., 2012].

The consequences of perinatal stress include deterioration of the body's neuroprotective potential. i.e., decreases in neurotrophin levels, in particular, BDNF. At the neurotransmitter level, there is a shift in the balance of excitatory and inhibitory processes. As in the pharmacological and hypoxia models listed above, investigators have reported decreased GABAergic system activity; extensive data also indicate an increase in the efficiency of glutamatergic transmission [Weinstock et al., 2017; Crombie et al., 2021].

At the morphological level, prenatal stress causes changes in the macro- and microstructure of components of the limbic system: the prefrontal cortex, amygdala, hippocampus, nucleus accumbens, cingulate gyrus, and other areas involved in regulating emotional behavior, stress reactivity, and other important functions [Charil et al., 2010; Weinstock et al., 2011, 2015]. As a result, offspring in "classical" models are characterized by increased anxiety and the presence of marked depressive-like behavioral manifestations, as well as cognitive and social impairments, which again indicates similarity of the mechanisms mediating the development of the sequelae of relatively selective perinatal

effects and generalized maternal and fetal distress [Charil et al., 2010].

In all the models discussed, behavioral disturbances persist not just to puberty in the animals (approximately two months), but also subsequently, indicating the severity and sometimes irreversibility of deviations, the difficulties of compensating for them (in the human case, this applies to problems and difficulties in psychological, pedagogical, and pharmacological correction). Assessment of the picture of the sequelae of perinatal stress is often complicated by concomitant disorders in fetal development and the birth process – premature birth, low neonatal weight, and anatomical anomalies. At the same time, the growth in the number of publications and general interest in this field of physiology and pathophysiology indicates the relevance of studying the relationship between exposure to perinatal stress and increases in the risk of early developmental disorders, as well as various abnormalities and pathologies in adulthood.

Conclusions. Summarizing the above data, we can conclude that pathological perinatal stress, largely regardless of the cause, has a critical impact on the developing nervous system. Results obtained from experimental animals show a high degree of similarity with the clinical characteristics of perinatal pathology in neonates at the behavioral, structural, cellular, and molecular levels.

Modeling of perinatal pathology in vivo in rodents by physicochemical modulation of CNS development processes is a universal tool for:

(a) studying the pathological states of the body and nervous system of neonates;

(b) seeking methods for correcting and compensating for CNS developmental disorders.

In our studies, use of various regulatory peptides is regarded as such a method: ACTH analogs and fragments, β-caseins, vasopressin, oxytocin, etc. This area is outside the scope of the present article; it should, however, be noted that peptide molecules are known to have a number of important advantages from the point of view of their prospects for clinical application: actions via specific receptor mechanisms, the possibility of triggering long-term "cascade" effects, and low toxicity. Identification of common pathways for perinatal disorders of different natures and the presence of similar symptoms allow us to consider regulatory peptides as relatively universal factors for correcting perinatal stress effects, ultimately reducing the risk of developing severe sensorimotor, cognitive, and psychoemotional pathologies.

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