REVIEW ARTICLE

Perinatal hypoxia as a risk factor for psychopathology later in life: the role of dopamine and neurotrophins

Ioanna Giannopoulou[1] · Marianna A. Pagida[2,3] · Despina D. Briana[4] · Maria T. Panayotacopoulou[2,3]

Abstract

Brain development is influenced by various prenatal, intrapartum, and postnatal events which may interact with genotype to affect the neural and psychophysiological systems related to emotions, specific cognitive functions (e.g., attention, memory), and language abilities and thereby heighten the risk for psychopathology later in life. Fetal hypoxia (intrapartum oxygen deprivation), hypoxia-related obstetric complications, and hypoxia during the early neonatal period are major environmental risk factors shown to be associated with an increased risk for later psychopathology. Experimental models of perinatal hypoxia/ischemia (PHI) showed that fetal hypoxia—a consequence common to many birth complications in humans—results in selective long-term disturbances of the dopaminergic systems that persist in adulthood. On the other hand, neurotrophic signaling is critical for pre- and postnatal brain development due to its impact on the process of neuronal development and its reaction to perinatal stress. The aim of this review is (a) to summarize epidemiological data confirming an association of PHI with an increased risk of a range of psychiatric disorders from childhood through adolescence to adulthood, (b) to present immunohistochemical findings on human autopsy material indicating vulnerability of the dopaminergic neurons of the human neonate to PHI that could predispose infant survivors of PHI to dopamine-related neurological and/or cognitive deficits in adulthood, and (c) to present and discuss older and recent findings on the differential expression of neurotrophins (BDNF, NGF, NT-3, and NT-4) in neonates following hypoxic/ischemic insults and its significance for the development of the human brain and the induction of psychopathology later in life.

Keywords Attention deficit hyperactivity disorder · BDNF · Dopamine · Neonate · Neurotrophins · Perinatal hypoxia · Schizophrenia · Tyrosine hydroxylase

Introduction and epidemiological data

A complex interplay of genetic and environmental factors is intricately involved in brain development; therefore, any disruption of these factors is capable of impacting upon neuronal structure, function, and connectivity and can thus alter the natural stages of development. In turn, this can result in long-lasting and even permanent effects and conduce to psychiatric disorders [1]. A range of prenatal, intrapartum, and postnatal events are likely to contribute to neurodevelopment

✉ Maria T. Panayotacopoulou
mpanagiot@med.uoa.gr

Ioanna Giannopoulou
igioannag@gmail.com

Marianna A. Pagida
marianna_pagida@yahoo.gr

Despina D. Briana
brianadespina@yahoo.com

[1] 2nd Department of Psychiatry, National and Kapodistrian University of Athens, Athens, Greece

[2] 1st Department of Psychiatry, National and Kapodistrian University of Athens, Athens, Greece

[3] Laboratory of Neurobiology and Histochemistry, University Mental Health Research Institute, PO Box 66517, GR-15601 Papagou, Athens, Greece

[4] Neonatal Unit, 1st Department of Pediatrics, National and Kapodistrian University of Athens, Athens, Greece

through interacting with the individual's genotype to affect the neural and psychophysiological systems related to emotion, specific cognitive functions (e.g., attention, memory), and language abilities, thereby heightening the risk for developing psychopathology later in life [2, 3].

Epidemiological studies indicated that fetal hypoxia (intrapartum oxygen deprivation), hypoxia-related obstetric complications, and hypoxia during the early neonatal period are among the biological environmental risk factors that have been hypothesized to play a role in the pathogenesis of schizophrenia, attention deficit hyperactivity disorder (ADHD), and autism spectrum disorders (ASD) [4–6]. Due to the great variety of causes inducing perinatal hypoxia, there are no published data on the overall incidence of perinatal hypoxic events. Estimates are quite variable depending on the definition used. De Haan et al. reported an incidence of perinatal asphyxia of 1 to 6 per 1000 live full-term births [7]. The overall incidence of fetal hypoxia/acidosis, however, as defined by the incidence of newborn metabolic acidosis, varies substantially between different European hospitals depending on the risk characteristics of the population and on labor management strategies. Reported rates based on newborn metabolic acidosis vary between 0.06 and 2.8% [8].

Early case-control studies involving patients with neurodevelopmental or psychiatric disorders and siblings or normal comparison groups have demonstrated a positive association between obstetric complications (OCs)/pregnancy and delivery complications (PDCs) and serious neurodevelopmental disorders (e.g., cerebral palsy, epilepsy, intellectual disability) [9], autism [10], childhood and adult schizophrenia [11–13], and a possible association with cluster B (such as borderline or antisocial) personality disorders later in life [14]. Studies focusing on specific childhood syndromes indicated that disruptive behavior disorders, i.e., ADHD, conduct disorder, and oppositional disorder, were associated with OCs/PDCs [15]. However, this type of study design did not help to clarify whether the observed association between psychiatric disorders and OCs/PDCs points to a causative contribution (true risk factors) or represents an outcome associated with a primary abnormality in the genetically susceptible fetus. The use of a broadly defined single OCs index did not allow for differentiation between the effects of various OCs/PDCs and hence contributed to inconsistent findings [16].

Subsequent population-based cohort studies shed more light on this topic through differentiating between the effects of various OCs/PDCs and adjusting for potential confounders [17–19]. Findings from a large long-term prospective study from the prenatal period through age 7 years and age 18 to 27 years—which examined the hypothesis that PDCs result in increased risk for the development of psychiatric disorders—showed that chronic fetal hypoxia doubled the risk of developing a psychotic disorder but failed to confirm prior reports of a positive association between either preterm birth or other PDCs and an adult psychiatric disorder [20]. Mild to severe cognitive impairment was

associated with preterm birth as well as chronic fetal hypoxia. Subsequently, a study conducted by Cannon and colleagues (2000) found that the odds of schizophrenia increased linearly with the increasing number of hypoxia-associated obstetric complications and that this effect was specific to cases with an earlier age at onset [21]. Signs of asphyxia at birth were independently associated with an increased risk of schizophrenia, while the odds ratios were approximately the same when divided into slight (OR 2.6; 95% CI, 1.3–5.3) or moderate to severe asphyxia (OR 2.8; 95% CI, 1.0–7.4). Evidence of increased vulnerability to effects of fetal hypoxia was also found in the 1991–1992 UK birth cohort study [22], which examined the presence of non-clinical psychotic experiences during childhood. More specifically, the risk of developing definite psychotic-like symptoms, which may increase the risk of developing clinically important psychotic disorders later in life [23, 24], was associated with the need for resuscitation at birth (adjusted OR 1.50, 95% CI, 0.97–2.31) and a lower 5-min Apgar score (adjusted OR per unit decrease 1.30, 95% CI, 1.14–1.51). The Swedish population-based cohort study [25], using as an outcome measure hospitalization for adult-onset (age > 16 years) psychiatric disorders, addressed the issue of whether preterm birth, intrauterine growth restriction, and delivery-related hypoxia, all associated with schizophrenia, also pertain to other adult-onset psychiatric disorders or whether these perinatal events are independent. The findings suggested that individuals with younger gestational age at birth (< 32 weeks) were 2.5 (95% CI, 1.0–6.0) times more likely to have a non-affective psychosis, 2.9 (95% CI, 1.8–4.6) times more likely to have depressive disorder and 7.4 (95% CI, 2.7–20.6) times more likely to have bipolar affective disorder. Similar associations were not observed for non-optimal fetal growth. With regard to delivery-related hypoxia, as indicated by a low 5-min Apgar score, only cases with a score of 3 or less were 2.2 (95% CI, 1.8–4.6) times more likely to have been hospitalized with depressive disorder and 3.8 (95% CI, 1.8–4.6) times more likely to have been hospitalized with bipolar affective disorder.

Fetal hypoxia places the developing brain at risk and could thus increase the chance of developing neuropsychiatric disorders that are diagnosed during early childhood, such as ASDs and ADHD [10]. A recent comprehensive meta-analysis conducted by Gardener, Spiegelman and Buka (2011) identified several perinatal risk factors, all associated with hypoxia before, during or immediately after birth, as increasing the risk of developing ASD [26]. The increased odds ratios (3.0 or more) were found for neonatal anemia (OR 7.87, 95% CI, 1.43–43.36), meconium aspiration (OR 7.34, 95% CI 2.30–23.47), birth trauma (OR 4.90, 95% CI, 1.41–16.94), and very low (< 1.5 kg) birth weight (OR 3.0, 95% CI, 1.73–5.20). Although fetal hypoxia has not been proven as an independent risk factor for ASD, its plausible role in the trajectory towards developing ASD needs to be clarified in future studies [10].

Adverse effects of perinatal obstetrical complications and prematurity have been shown to be associated with ADHD. A case-

control study found higher rates of pregnancy, labor/delivery, and neonatal complications in children diagnosed with ADHD as compared to their unaffected siblings. Of particular interest was the finding that having received oxygen therapy—clearly indicating hypoxia during the first 2 months of life—increased the risk of developing ADHD [27]. A recent nested case-control cohort study, using the Kaiser Permanente Southern California electronic medical records, indicated that exposure to perinatal hypoxia/ischemia (PHI), and in particular to birth asphyxia, neonatal respiratory distress syndrome, and preeclampsia, was associated with a 16% greater risk of developing ADHD. Specifically, exposure to birth asphyxia was associated with a 26% greater risk of developing ADHD; exposure to neonatal respiratory distress syndrome was associated with a 47% greater risk, and exposure to preeclampsia was associated with a 34% greater risk. The increased risk of ADHD remained the same across all race and ethnicity groups [28].

The role of perinatal hypoxia in human brain dopamine neurotransmission

Since dopaminergic mechanisms are central to both ADHD [29] and schizophrenia pathophysiology [30, 31], the effect of perinatal hypoxia on dopamine neurotransmission was studied in the human neonatal brain at autopsy [32, 33] as well as in experimental animals from birth to adulthood [34–37]. Animal models of PHI showed that hypoxic/ischemic lesions can cause selective long-term changes to the central dopaminergic systems that persist into adulthood [34, 36, 38]. The substantia nigra (SN) and the ventral tegmental area (VTA) in the mesencephalon contain the majority of dopaminergic neurons in the brain and are heavily involved in the control of motor and cognitive behaviors.

Studies on human autopsy material showed that PHI—depending on its severity/duration—differentially affects the cellular and molecular mechanisms that regulate the synthesis of tyrosine hydroxylase (TH), the first and rate-limiting enzyme of dopamine synthesis, in different catecholaminergic brain nuclei [32, 39–42]. TH is an oxygen-requiring enzyme, and kinetic properties suggest that oxygen availability may limit the synthesis of catecholamines in the brain [43]. TH, however, loses its oxygen dependency during physical stress, indicating that substrate limitation can be overcome when the neuronal needs for the neurotransmitter are increased [43, 44]. Hypoxia is a major regulator of TH gene expression. Several transcription factors that are activated by hypoxic conditions (e.g., hypoxia inducible factor-HIF-1) can regulate both the rate of TH expression and TH mRNA stability [45, 46]. Interestingly, Schmidt-Kastner and colleagues found that 55% of schizophrenia candidate genes are regulated by hypoxia and/or expressed in the vascular system [47].

The mesencephalic dopaminergic neurons of the neonate are especially vulnerable to prolonged PHI [32], as indicated by immunohistochemistry on postmortem material of the SN and VTA obtained at autopsy of 16 full-term and two preterm neonates after parental written consent (Greek Brain Bank, directed by Professor of Pathology University of Athens, E. Patsouris). The estimation of the severity/duration of the PHI injury was based on established neuropathological criteria [48–50], taking into consideration the regional aspects of neuronal necrosis [39] (performed by perinatal pathologist, Prof. A. Konstantinidou).

In neonates with neuropathological signs of abrupt PHI injury, intense TH-immunoreactivity was found in the SN and VTA [32]. Interestingly, increased TH-immunoreactivity and increased in vivo synthesis of dopamine have been reported in the SN of patients with schizophrenia using neuroimaging techniques [31]. In neonates who suffered an abrupt PHI however, TH expression was also observed in neurons synthesizing urocortin-1 (a stress peptide belonging to the corticotropin-releasing factor family) of the Edinger-Westphal nucleus, a nucleus not previously known for its dopaminergic phenotype [32, 42]. Edinger-Westphal plays a significant role in stress response and, therefore, in stress-related disorders like anxiety and major depression, as well as in regulation of food and water intake and the use of alcohol and drugs of abuse.

In the same sample, neonates with neuropathological changes of prolonged or older PHI damage showed a striking reduction of TH-immunoreactivity in the mesencephalic dopaminergic neurons, pointing to possible early dysregulation of dopaminergic neurotransmission under prolonged hypoxic conditions. SN neurons were found to be of a significantly smaller size in the above cases compared to those of neonates with acute PHI injury [32], raising the question whether this significant decrease in both their size and their ability to synthesize dopamine reflects an early stage of degeneration or a developmental delay of dopaminergic neurons. Abnormal maturation of the SN has been described in ADHD [51], while a substantial reduction in the volume of the nigrostriatal area accompanied by a decreased size of SN neurons has been reported in schizophrenia [52]. Degeneration of the SN and inhibition of dopamine synthesis are the main neuropathological findings in Parkinson's disease [53].

The results of studies investigating the human mesencephalon are in agreement with experimental data indicating that PHI causes duration-dependant changes in the number of the dopaminergic neurons in the SN and VTA as well as in DA neurotransmission in their target areas (summarized in Table 1). An increased number of dopaminergic neurons were observed in the SN and VTA of the rat after a brief perinatal hypoxic insult [34, 37]. Unilateral hypoxic/ischemic injury in the neonatal rat resulted in a persistent increase in the density of striatal TH immunoperoxidase staining in the ipsilateral site [54]. In addition, perinatal hypoxia induced structural changes in the developing brain, i.e., shrinkage of the hippocampus

Table 1 Table summarizing immunohistochemical studies concerning the effect of PHI on the expression of TH in the mesencephalic dopaminergic neurons and their target areas

Material/experimental model	Severity/duration of PHI	Postnatal age after PHI	Results/brain region
Rat/unilateral carotid ligation at PD 7or 8	8% oxygen for 3.5 h	3–4 weeks and 9–12 weeks	↑ TH-IR fibers in striatum and nucleus accumbens [54]
Rat/delayed cesarean section (whole uterus in water)	14–17 min	3 weeks	↑ number of TH-IR cell bodies in substantia nigra [34]
Rat/unilateral carotid ligation at PD 7 or 8	8% oxygen for 3 h	8–12 weeks	↓ number of TH-IR cell bodies in substantia nigra [36]
Rat/delayed cesarean section (whole uterus in water)	15–22 min	4 weeks	↑ number of TH-IR cell bodies (after 15–20 min asphyxia) in substantia nigra and ventral tegmental area [37] ↓ number of TH-IR cell bodies (after asphyxia longer than 20 min) in substantia nigra and ventral tegmental area [37]
Human/postmortem brain material	Based on neuropathological criteria	0–130 days	↑ TH-immunoreactivity after severe/acute PHI in substantia nigra, ventral tegmental area, and Edinger-Westphal nucleus [32] ↓ or no TH-immunoreactivity after prolonged PHI in substantia nigra, ventral tegmental area, and Edinger-Westphal nucleus [32]

PHI, perinatal hypoxia/ischemia; *TH*, tyrosine hydroxylase; *h*, hours; *IR*, immunoreactive; *PD*, postnatal day; *min*, minutes, ↑, increase; ↓, decrease

and the superimposing frontal cortex in the ipsilateral site as well as ventricular enlargement. Similar structural abnormalities (i.e., reduction of the brain volume in the hippocampus/prefrontal cortex and ventricular enlargement) accompanied by abnormal dopaminergic neurotransmission) are repeatedly reported in individuals suffering from schizophrenia [55–57] or ADHD [58–60].

Since experimental studies have shown that PHI can cause long-lasting alterations in the central dopaminergic systems that persist into adulthood [36, 38], we considered that dysfunction of dopaminergic systems in the early developmental stages can predispose the survivors of PHI to dopamine-related neurological and neurodevelopmental psychiatric disorders later in life [32, 61]. Dopamine-mediated signaling plays a fundamental neurodevelopmental role in forebrain differentiation and circuit formation. These developmental effects, such as modulation of neuronal migration and dendritic growth, occur before synaptogenesis and demonstrate novel roles for dopaminergic signaling beyond neuromodulation at the synapse [1].

The role of perinatal hypoxia in neurotrophin signaling

Dopamine—as well as other neurotransmitter systems reported to be dysregulated by perinatal hypoxia in experimental animals, such as serotonin [62] and noradrenaline [63]—express their developmental roles partially through their interaction with neurotrophins [64, 65]. Recent emerging evidence suggests disrupted neurotrophic signaling in response to perinatal hypoxia in the molecular pathogenesis of later psychopathology, possibly indicating neurotrophins as novel molecular targets for preventive intervention [66–69]. Thus,

neurotrophins are currently prominent candidates for mediating the relationship between perinatal hypoxia and psychopathology due to their critical role in protecting against neuronal damage following adverse intrauterine events [70], their documented dysregulation in neuropsychiatric disorders [66, 69], and their abnormal expression in response to fetal hypoxia [67].

Members of the neurotrophin family, including the nerve growth factor (NGF), the brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), and neurotrophin-4 (NT-4) play a fundamental role in brain function and neuroprotection [71]. They are important for axon growth, higher neuronal functions, developmental maturity of the cortex, and synaptic plasticity, leading to refinement of connections, morphologic differentiation, and neurotransmitter expression [71]. Neurotrophic factors play crucial roles in neuroprotection by promoting survival and by reducing apoptosis in many neuronal populations [71, 72] and are therefore critical for pre- and postnatal brain development. In an experimental model, perinatal circulating levels of neurotrophins reflected central nervous system (CNS) levels due to immaturity of the blood-brain barrier [73].

During fetal development, the expression of neurotrophins and their receptors significantly increases at times of maximal neuronal growth, differentiation, and synaptogenesis [74]. Studies performed in rodents have shown that the expression of NGF and BDNF is developmentally localized in the hippocampus and prefrontal cortex, two regions which play a key role in psychiatric disorders and that are well-studied sites of both developmental and adult synaptic plasticity [74]. Changes in the expression of these neurotrophins at critical times during development could promote a cascade of events interfering with maturation of these regions, setting the stage for altered responsiveness to stress in adulthood [75]. Potential

sources of fetal BDNF in humans may be endogenous fetal synthesis, maternal passage, and/or placental production [76]. Cord blood BDNF increases with advancing gestational age, probably corresponding to the fourfold increase of human cortical gray matter between 29 and 35 weeks of gestation with increasing synaptic maturity [77, 78]. Similarly, a human study provides evidence that cord blood NGF levels are higher in full-term than in preterm infants, probably reflecting the differential degree of peripheral and CNS maturity [77]. Further upregulation of circulating BDNF levels beyond the first week of life correlates with factors influencing neurodevelopmental outcomes [76].

During the perinatal period, neurotrophins present with different patterns of changes according to their impact on the process of neuronal development and their reaction to perinatal stress [79]. BDNF is involved in critical developmental processes of the nervous system, including proliferation, migration, differentiation, and synaptogenesis [80] while regulating placental growth and development, as observed in both human and animal studies [81, 82]. BDNF also ensures survival of existing neurons under stressful conditions, such as fetal hypoxia [80, 83]. BDNF, NGF, and their receptors are strongly upregulated following hypoxic/ischemic insults [84]. Treatment studies in animals, using BDNF and NGF, have shown that both these factors offer significant neuroprotection against delayed neuronal death following hypoxic/ischemic neonatal brain injury [70].

Besides acute hypoxic conditions, neurotrophic factors present with an altered pattern of expression and function in clinical states of prolonged perinatal hypoxia, such as intrauterine growth restriction (IUGR) and maternal diabetes, which are strongly associated with later development of neuropsychiatric disorders [85, 86]. Experimental studies suggest that BDNF is downregulated in the fetal hippocampus in chronic placental insufficiency [87], a common cause of

IUGR. It seems that IUGR changes the time course of fetal BDNF production in specific hippocampal and hypothalamic areas during sensitive developmental windows [87]. Furthermore, lower levels of the BDNF receptor have been demonstrated in cortical neurons of IUGR rats, leading to reduced cell viability and synaptic function and possibly playing a role in schizophrenia-like behaviors [88]. Similarly, a human study points to downregulation of NGF in IUGR fetuses/neonates [89]. By contrast, higher placental BDNF expression has been documented in both IUGR rats and humans, probably representing a regulatory mechanism required to counterbalance the restriction of fetal growth [90]. A recent clinical study provides serologically based prospective evidence of abnormal fetal expression of BDNF in response to maternal diabetes, probably implicated in the association between diabetes in pregnancy and later neurodevelopmental disorders in the offspring [91].

Likewise, placentas from diabetic pregnancies exhibited decreased mRNA expression of BDNF in cases of fetal macrosomia [90]. Furthermore, previous data indicated that birth hypoxia was associated with a significant (20%) decrease in cord blood BDNF among individuals who developed schizophrenia as adults, while birth hypoxia was associated with a significant (10%) increase in BDNF among control subjects. This differential response of BDNF to fetal hypoxia was specific to schizophrenia and was not explained by other obstetric complications or by the BDNF valine (val) to methionine (met) polymorphism at codon 66 (val66met) [67].

Abnormal BDNF gene activity is a leading etiological hypothesis which proposes that early-life adverse experiences may persistently modify brain and behavioral plasticity. Overall, early-life disruptive events influence BDNF gene activity and behavioral outcome [68]. Prenatal stress has been shown to increase BDNF methylation of both exons IV and VI of the BDNF gene in rats, implying that the decreased

Table 2 Table summarizing published data concerning the physiological changes and the effect of PHI on BDNF expression in various sources/time points throughout fetal/neonatal development

Sources time points	Human blood	Human placenta	Animals	References
Before birth	↑		↓ in hippocampus in IUGR	[77, 78, 87]
At/after birth	↓	↑ in IUGR	↑ in PA	[83, 84, 90–92]
	↑ in PA (CSF)	↓ in diabetic/non-diabetic macrosomia	↓ in diabetic/non-diabetic macrosomia	
	↓ in diabetic/non-diabetic macrosomia			
	↑ DNA methylation in perinatal stress			
First day	↓		↓ in cortical neurons in IUGR	[87]
1st week	↑			[76, 79]

PHI, perinatal hypoxia/ischemia; *PA*, perinatal asphyxia; *CSF*, cerebrospinal fluid; *IUGR*, intrauterine growth restriction

expression of BDNF in offspring exposed to prenatal stress may be mediated by increased BDNF methylation [92]. Recent interesting findings, pertinent to both humans and animals, suggest that BDNF DNA methylation in the blood may be used as a predictor of brain BDNF DNA methylation and gene expression, as well as of behavioral vulnerability induced by early-life environmental exposure. The authors propose that since BDNF expression and DNA methylation are altered in several psychiatric disorders that are associated with early-life adversity, including depression, schizophrenia, bipolar disorder, and autism, BDNF DNA methylation in the blood may represent a novel biomarker for the early detection of psychopathology [93]. Published data on physiological changes of BDNF expression and the effect of PHI are summarized in Table 2.

In conclusion, current evidence suggests that dysregulation of dopaminergic neurotransmission, as well as changes in the expression and action of neurotrophins as a result of early adverse experiences, such as PHI, could exert both short- and long-term effects on neurobehavioral plasticity, resulting in an increased propensity for psychopathology in adulthood. Further studies are required to elucidate the significance of dopamine and neurotrophins during the perinatal period and especially in relation to factors that may cause neurologic insults in the developing brain and predispose to neuro- and psychopathology in later life.

Compliance with ethical standards

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