Impact of Perinatal Hypoxia on the Developing Brain

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Short title: Perinatal Hypoxia: Causes and Consequences

Summary

Perinatal hypoxia is still one of the greatest threats to the newborn child, even in developed countries. However, there is a lack of works which summarize up-to-date information about that huge topic. Our review covers a broader spectrum of recent results from studies on mechanisms leading to hypoxia-induced injury. It also resumes possible primary causes and observed behavioral outcomes of perinatal hypoxia. In this review, we recognize two types of hypoxia, according to the localization of its primary cause: environmental and placental. Later we analyze possible pathways of prenatal hypoxia-induced injury including gene expression changes, glutaminergic excitatory damage (and a role of NMDA receptors in it), oxidative stress with ROS and RNS production, inflammation and apoptosis. Moreover, we focus on the impact of these pathophysiological changes on the structure and development of the brain, especially on its regions: corpus striatum and hippocampus. These brain changes of the offspring lead to impairments in their postnatal growth and sensorimotor development, and in their motor functions, activity, emotionality and learning ability in adulthood. Later we compare various animal models used to investigate the impact of prenatal and postnatal injury (hypoxic, ischemic or combinatory) on living organisms, and show their advantages and limitations.

Keywords: excitotoxicity, ROS, hypoxic model, emotionality, cognition

Perinatal Hypoxia

The precise course of the gravidity, birth, and the early postnatal period are necessary for the healthy maturation of the newborn child. Lowered oxygen supply (hypoxia), a complete arrest of gas exchange in lungs (asphyxia), or insufficient blood, oxygen, and nutritional supply (ischemia) during these vulnerable periods are some of the most prominent causes of their death and morbidity (Vlassaks *et al*. 2013). Developing fetus undergoes a heightened risk of hypoxia during the prenatal period when morphological differentiation of the brain and neuronal circuits occurs, but also during labor and transition to autonomous breathing (Landry *et al*. 2014). As the oxygen level is physiologically low in the fetal blood, the fetus does not react to a hypoxic insult with a "fight or flight" reaction, but in the opposite way. The fetus gets immobilized, has lowered metabolism and thermogenesis, increased level of blood catecholamines and glucocorticoids (with the following redistribution of blood circulation to vital organs) and stops breathing movements (Herlenius and Lagercrantz 2004; Landry *et al*. 2014). Hypoxia of the fetus or newborn is one of the main causes of fetal cerebral damage and abnormal development of the brain that can manifest in adulthood as problems with learning, memory, and attention (Kaur *et al*. 2008). Gestational hypoxia can also induce seizure activity and changes in brain neurotransmitter levels that impact the behavior of the offspring (Glass *et al*. 2011). Birth complications are also being connected to neurodevelopmental disorders, such as schizophrenia, ADHD, autism, cerebral palsy and periventricular leukomalacia (Golan *et al*. 2009; Howell and Pillai 2014).

Long-lasting hypoxia weakens cardiac function, lowers blood pressure, and leads to bradycardia. The failing cardiovascular system is no longer able to offer sufficient blood- and nutritional supply to tissues and ischemia occurs. The presence of ischemia dramatically worsens the impact of hypoxia and lowers the neuronal chances to survive. Depression of the partial oxygen pressure in tissues is related to lowered glucose levels that may lead to a decrease in the availability of energy for cells, neuronal deterioration, and death (de Courten-Myers *et al*. 2000). Although hypoxia-ischemia is not very common in children

born in the term, more than half of preterm infants and low-birth-weight newborns suffer from it (Delcour *et al*. 2012).

Causes of Prenatal Hypoxia

Changes to the internal environment of a mother, as well as placental function deterioration, can be the causes of brain injury of the offspring. Prenatal hypoxia can be, according to the localization of its cause, divided into two types:

1. Environmental hypoxia – both mother and fetus are hypoxic, the cause is a change in the external or maternal environment.
2. Placental hypoxia – the mother is normoxic, but the fetus is hypoxic because of a placental impairment.

Factors that contribute to hypoxia *in utero* include serious long-lasting maternal illnesses, such as impairment in the function of heart, lungs, and kidney (Gonzalez-Rodriguez *et al*. 2014), anemia, hemoglobinopathy (Patterson and Zhang 2010) and gestational diabetes (Curtis *et al*. 2014). The risk of hypoxia is also augmented by gravidity in high altitudes (over 2500 meters above the sea level), environmental pollution, pre-eclampsia, maternal smoking, alcohol consumption, or administration of glucocorticoids to the mother (Sandau and Handa 2007). Maternal stress, especially the traumatic one, activates hypothalamus-pituitary-adrenal axis that augments cortisol and cytokine production and directs the blood flow in the maternal organism to skeletal muscles leading to lowered perfusion of the uterus and the fetus (Curtis *et al*. 2014). Strong maternal stress can even lead to the constriction of the umbilical artery and ischemia of fetus.

The prenatal growth of fetus depends on the normal placental function and the ability of oxygen and nutrients to cross from maternal bloodstream to the blood of the fetus. Short episodes of hypoxia *in utero* may be caused by a broad spectrum of incidents that reduce the maternal blood flow through the placenta,

for example, umbilical cord compression, detachment of the placenta, or depression of blood perfusion through the placental intervillous place (Rong Guo *et al*. 2010; Wang *et al*. 2016). Strong contractions of the uterus may also lead to episodes of bradycardia and hypotension of the fetus that may cause serious brain hypoperfusion and consecutive damage to the brain tissue (Jain *et al*. 2015). During birth, hypoxia can occur as a result of obstetric complications and the following contraction of the uterus, eclampsia, or the disrupted blood supply to the fetus caused by umbilical cord compression (Golan *et al*. 2009).

Chronic hypoxemia can also be caused by defective placentation, failure in placental development, or perturbation of its function (Rong Guo *et al*. 2010; Wang *et al*. 2016). Morphological changes of the hypoxic placenta differ depending on the primary cause of hypoxia: enlargement of a placenta suggests a lowered content of oxygen in the bloodstream of the mother, while small placentas indicate that the cause of the fetal hypoxia might be its underdevelopment (Eskild et al. 2016). Hypoxia may also affect the supply of nutrients to the fetus by inhibition of placental rapamycin complex 1 (mTORC1) responsible for the growth, proliferation, and metabolism of cells (Kimball et al. 2015). During prenatal hypoxia, lower availability of essential amino acids (mainly phenylalanine, tyrosine, and serine) may occur because of their lowered placental transport and elevated catabolism for the generation of energy (Jansson and Powell 2007).

The primary cause of brain damage during prenatal hypoxia can also be the placenta itself. One of the defensive placental mechanisms against toxins or changed oxygen supply is a secretion of factors that elevate intracellular content of calcium and lead to the generation of free radicals in neurons of the developing embryo. This placental secretion is also accountable for changes in glutamate levels in the brain of the fetus and lowered synaptic density, dendritic length and branching complexity of neurons in the developing brain (Curtis *et al*. 2014).

Mechanisms of Injury and Reactions to Hypoxia

A great similarity in reactions to hypoxia between various animal species implicates their common compensational mechanisms during development. The exact way, how transient complications during gestation lead to diseases later in life, is, however, still unclear.

Shortage of oxygen negatively affects cerebral oxidative metabolism and, in serious cases, it can even lead to depletion of energy reserves in tissues. Hypoxia leads to cascades of neurotoxic biochemical processes, such as alterations in membrane potential and ion distribution, nitric-oxide production, accumulation of reactive oxygen species and excitatory amino acids in the extracellular area and inflammation (Esih *et al*. 2017; Sab *et al*. 2013) (ABHIJIT S, SUBRAMANYAM MVV, DEVI SA: Grape seed proanthocyanidin and swimming exercise protects against cognitive decline: a study on m1 acetylcholine receptors in aging male rat brain. *Neurochem Res* **42**: 3573-3586, 2017.

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Figure 1). Anaerobic cellular metabolism is also activated during the hypoxic period. Accumulation of its product – lactate – leads to metabolic acidosis that negatively affects cellular viability. Chronic hypoxemia, raised lactate/pyruvate ratio and a decline in antioxidant mechanisms lead to up-regulation of pro-apoptotic genes, apoptosis and therefore to decrease in numbers of neurons in the fetal brain (Rong Guo *et al*. 2010).

HIF-1 and Gene Expression Changes

Hypoxia activates compensatory mechanisms in cells, including the temporary arrest of the cell cycle, lowered energy consumption and secretion of factors needed for survival and angiogenesis. The main transcriptional factor that controls the response to hypoxia is hypoxia-inducible factor 1 (HIF-1). HIF-1 is a heterodimer consisting of two alpha and two beta subunits. HIF-1α is physiologically degraded by an ubiquitin-proteasome complex that prevents its accumulation in tissues (Brown et al. 2016). This

degradation is induced by a prolyl hydroxylase, which activity depends on a continuous supply of oxygen (Clerici et al. 2002). Therefore, the hydroxylation and degradation of HIF-1α do not occur during hypoxia. Stabilized HIF-1α is translocated to the nucleus and heterodimerizes with the beta subunit. HIF-1 heterodimer can than bind to a hypoxia-responsive element localized in promoters of more than a thousand genes induced by hypoxia (Brown et al. 2016). Authors Lim et al. (2010) suggest sirtuin-1 (SIRT1) may provide a positive feedback loop that maintains a high level of HIF-1 activity during hypoxia. SIRT1 activation also plays important role in mediation of hyperbaric oxygen preconditioning associated ischemic tolerance (Ding et al. 2017). Stabilized HIF-1 induces expression of genes responsible for cellular adaptation from normoxia to hypoxia and therefore allows their survival. Many glycolytic enzymes, as well as glucose transporters, are up-regulated by HIF-1 as an adaptive response to lowered oxygen levels. Other HIF-1-regulated genes erythropoietin and vascular endothelial growth factor (VEGF) amplify blood vessel permeability and thereby facilitate brain perfusion (Howell and Pillai 2014). HIF-1 also induces expression of various isoforms of NO-synthases that are responsible for nitric oxide synthesis and vasodilatation (Kaur et al. 2008). Changes in blood vessels following hypoxia acutely contribute to neuronal protection; however, as they increase metabolic needs, if they last for too long, they may aggravate the vulnerability of the developing brain.

Excitatory Damage

Glutamate and aspartate are the principal excitatory amino acids, and they are the main neurotransmitters in half of the synapses in the mammalian frontal cortex (Cooper *et al*. 2003). Excitatory amino acids have a broad spectrum of physiological functions during CNS development. They are necessary for growth and regulate the survival and differentiation of neurons (Gadirova and Agaev 2015). Neurotransmitter systems of excitatory amino acids also play a significant role in signal transmission, neuronal plasticity in synapses, learning, and memory. However, even a transient elevation of excitatory amino acids during hypoxia potentiates excitability and energetic demands of cells, which may be even aggravated in the presence of ischemia (Khashaba *et al*. 2006, Riljak *et al.* 2016). Elevated levels of glutamate were found

in the blood of many fetuses, who suffered from neurobehavioral changes later in life. Prenatal hypoxia elevates the number of glutamate receptors in frontal cortex and hippocampus (Howell and Pillai 2014) and significantly diminishes the number of cortical synapses and synaptic vesicles in adult mice. These changes may weaken plasticity and signaling ability of synapses that later leads to deterioration of learning and memory. Changes in glutamate signalization and excitatory synapses were also recorded in rats after perinatal hypoxia and seizures (McClendon *et al*. 2014).

NMDA Receptors

NMDA glutaminergic receptors, which are important for long-term potentiation and synaptic plasticity, dominate in the developing brain (Herlenius and Lagercrantz 2004). They also enable the development and migration of neurons and synapse formation (McClendon *et al*. 2014). However, this domination of NMDA receptors may harm the developing brain and make it more sensitive to hypoxia-induced excitotoxicity. Growing evidence links ROS production, phospholipase activation, inflammation, and mitochondrial dysfunction, to a cascade of NMDA effects on neurons (Burd *et al*. 2016; Li *et al*. 2018).

Hypoxia and ischemia destroy calcium homeostasis and lead to calcium-overload. As NMDA receptor is selectively permeable to Ca^{2+} ion, it may play a crucial role in hypoxia-induced neurotoxicity. Although this intake of calcium through NMDA receptors is inevitable for long-term potentiation, its elevated levels can damage neurons and induce transcription of pro-apoptotic proteins Bax, Bad and Bcl-xl (Savignon *et al*. 2012). Moreover, NMDA-receptor antagonists can alleviate neuronal damage *in vivo* and *in vitro* in experimental models of focal ischemia (Fan *et al*. 2015). However, intact rat fetuses that were subjected to NMDA-antagonists had elevated apoptosis in the brain, too. This fact led to a conclusion that elevation, as well as depression of NMDA-receptor activity, can be lethal to developing neurons (Herlenius and Lagercrantz 2004).

Oxidative Stress and ROS

Pathogenesis of the brain damage during intrauterine development may include many pathways of injury including the formation of reactive oxygen species (ROS). Oxidative stress is defined as the appearance of ROS in either non-physiological regions of the organism or in non-physiologically high concentrations (Curtis *et al*. 2014). Oxygen is the end-acceptor of electrons in the mitochondrial electron transport chain that is connected to oxidative phosphorylation and energy generation through ATP synthesis. If the oxygen supply is lowered or completely arrested, electron transport slows and therefore cannot completely fulfill the metabolic needs of cells (Patterson and Zhang 2010). Hypoxia also elevates ROS levels, as it deteriorates complex I and III of the mitochondrial electron transport system. Electrons in this transport system flow fast under physiological conditions. It diminishes the possibility of interaction of free radicals with molecular oxygen and subsequent superoxide-radical creation. In the hypoxic environment, the flow of electrons is slower and therefore the possibility of the formation of superoxide anion increases (Poyton *et al*. 2009). ROS destabilize membrane components, initiate apoptosis of neurons and damage the vascular system in the brain (Koundal *et al*. 2014). Fast re-oxygenation after hypoxia can destroy the fetal blood-brain barrier by a ROS generation and may, therefore, amplify the impact of molecules from the fetal blood on the brain. It may happen even in newborn, whose blood-brain barrier is more protective than that of the fetus (Curtis *et al*. 2014; Riljak *et al.* 2016).

Reactive Nitrogen Species (RNS)

As mentioned before, the expression of NO-synthase is elevated during hypoxia to maintain adequate cerebral perfusion. However, this accrual in NO production is cytotoxic and drastically facilitates the generation of free radicals (Savignon *et al*. 2012). NO radical can react with superoxide anion forming another very potent radical peroxynitrite. Overproduction of free radicals (especially hydroxyl radical and peroxynitrite) rapidly oxidizes proteins, lipids, and DNA, leading to cellular damage and death (Liu *et al*. 2011). Generation of ROS and RNS is also involved in cellular death leading to white matter injury in preterm newborns (Sab *et al*. 2013).

As a defense from oxidative stress, cells have antioxidant enzymes – manganese superoxide dismutase, glutathione peroxidase, and catalase - that detoxify free radicals and protect cells from injury. However, the activity of glutathione peroxidase is lowered in the developing brain, raising the possibility of oxidative damage to cells (Esih *et al*. 2017). A clinical study in children suffering from perinatal encephalopathy found lowered antioxidant levels and elevated lipid peroxidation during the first year of their life (Levitina 2001). Limiting oxidative stress following hypoxia/reoxygenation is important factor for attenuation of organ damage caused by free radicals (Gabrielová *et al.* 2015).

Inflammation

Microglia are the main immune cells in the CNS derived from monocytes that produce cytokines but are also able of phagocytosis (Delgado and Ganea 2003). In the developing brain, microglia are preceded by amoeboid microglial cells (AMC) that are localized mainly in the periventricular white matter. After activation by hypoxic insult, AMC proliferate, increase phagocytosis, actively migrate to the side of injury and release cytokines, chemokines, and NO, leading to the induction of inflammatory response (Hanisch and Kettenmann 2007). Postnatal hypoxia-ischemia (Ding *et al*. 2017), asphyxia (Vlassaks *et al*. 2013), as well as chronic hypoxia alone (Rong Guo *et al*. 2010), can acutely raise cytokine production and cause inflammation in animal models. Inflammation elevates ROS generation leading to tissue damage and neurological deterioration later in life. Neuronal loss, white matter damage and activation of immune cells in the CNS are the main hallmarks of hypoxic injury of the brain (Folkerth 2006). Post mortem studies of the human brain after perinatal injury also confirmed the presence of pro-inflammatory cytokines together with markers of oxidation (Robinson *et al*. 2005). It is supposed that cytokines (especially TNF-α) control lipid metabolism of the brain (Vlassaks *et al*. 2013), depress survival and maturation of oligodendrocytes (Robinson *et al*. 2005), and slow down the growth of the fetus (Rong Guo *et al*. 2010). They can also induce the activation of matrix metalloproteinases, the zinc-dependent enzymes that degrade the extracellular matrix and contribute to tissue remodeling (Oh *et al*. 2008).

Elevated release of pro-inflammatory cytokines is also connected to cardiac injury in preterm newborns and activates a death-receptor pathway that leads to cellular apoptosis (Nian 2004).

Cellular Death

In animal models, even a relatively short time of hypoxic exposure to the fetus can lead to the death of sensitive neuronal populations (for mechanisms see ABHIJIT S, SUBRAMANYAM MVV, DEVI SA: Grape seed proanthocyanidin and swimming exercise protects against cognitive decline: a study on m1 acetylcholine receptors in aging male rat brain. *Neurochem Res* **42**: 3573-3586, 2017.

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Figure 1) (Curtis *et al*. 2014). *Post mortem* study of human fetuses, who died around the time of birth, showed a premortal brain injury and neuronal loss caused by chronic placental problems (Rong Guo *et al*. 2010).

Neurons can undergo apoptotic, autophagic, or necrotic cell death, depending on the type and extent of the damage. Perinatal asphyxia usually leads to apoptotic cell death (Takada *et al*. 2015). The neuronal cell death has three stages: the first stage of early cellular death and brain injury is a consequence of depletion of cellular energy reserves resulting from lowered oxidative metabolism immediately after hypoxia (seconds to minutes) (Curtis *et al*. 2014). The second phase of neuronal damage occurs after few hours during reperfusion and reoxygenation as a result of free-radical formation, calcium entry to cells and apoptosis (McGuire 2007). This phase may continue for days. Some authors also suppose the existence of the third phase of the injury, which further worsens the resulting phenotype. For this phase,

especially inflammation and epigenetic changes are accountable, leading to impairment in axonal growth, neurogenesis, and synaptogenesis (Dixon *et al*. 2015). In general neurogenesis appears to be very sensitive to many types of stressors particularly when stress occurs during the early postnatal period and long-lasting effects might be manifested by affected cell survival (Raček et al. 2018).

Neuroplasticity

Brain plasticity is maximal in the first few years of life, but continues at reduced rate throughout life. Human brain is not fully mature until at least twenty years after birth. In this period the brain is highly dependent on experience and shaped and modified based on it. At birth, each neuron has 7500 connections. These increase rapidly and at the age of two years the number of connections is double of adult brain. Ultimately, pruning of synapses through the apoptosis and programmed cell death will shape the personality of the human being (Mundkur 2005). Although the developing brain is more plastic and thus would be expected to have better recovery mechanisms following injury, it seems that result of the higher plasticity might be both, beneficial as well as detrimental. The beneficial results of plasticity in the nervous system appear to be contingent upon the inciting stimuli. If we take into consideration the massive process of connection building and pruning, immature brain has some of the worst developmental outcomes following significant insult (Giza and Prins 2006). Even though the immature brain is more malleable to external stimuli compared to the adult one, a hypoxic-ischemic event to the neonate interrupts the shaping of central motor pathways and can affect normal developmental plasticity through altering neurotransmission, changes in cellular signaling, neural connectivity and function, wrong targeted innervation, and interruption of developmental apoptosis (for detailed review see Rocha-Ferreira and Hristova 2016).

Animal Models of Hypoxia

Models of Prenatal Injury

The brain of newborn mammals is considered to be more resistant to hypoxia and anoxia than the central nervous system of adult animals. As brain maturation proceeds during postnatal development resistance to various types of oxygen deficiency highly decreases. In neonatal brain there are auxiliary mechanisms that help to overcome problems connected with the high rate of lactate production (Drahota et al. 1980). In *in vivo* studies, pregnant animals usually have to be exposed to 8-12% oxygen that significantly reduces partial oxygen pressure in arteries of the fetus, as the normal pO2 of the fetus is similar to oxygen levels in arteries of adult hypoxic animals (Patterson and Zhang 2010). Mild hypoxia (oxygen content in the breathed air circa 15%) and medium hypoxia (10% of oxygen in the breathed air) is known to be non-lethal if not used overly during a too long period (Landry *et al*. 2014).

Rodent models of prenatal hypoxia apply either normobaric (Ujhazy *et al*. 2013) or hypobaric (Maresová *et al*. 2001) hypoxia to pregnant animals. Pregnant female rats are placed to the hypoxic or hypobaric chamber and exposed to lowered oxygen levels for the precisely defined period of the prenatal development of the fetus. This model replicates mainly lung diseases of the mother, sleep apnea, or other breathing-related disorders in humans (Ujhazy *et al*. 2013). Alternative models of chronic prenatal hypoxia are nitrite intoxication of pregnant females, or phenytoin administration (Mach *et al*. 2006). One disadvantage of these models of maternal hypoxia is, that although they show mainly the effect of prenatal hypoxia on the offspring, the impact of accompanying factors (such as higher levels of maternal stress hormones or reduced food intake of the mother during hypoxia) cannot be excluded.

Less-used model on chicks induces hypoxia by half-wrapping of eggs lengthwise for a specific period of fetal development. This egg-wrapping has the same effect as incubation of chicken embryos in a hypoxic environment, as the cover reduces oxygen supply to the developing embryo (Camm *et al*. 2005). The

advantage of this model is that it shows the "pure" effect of hypoxia without the additive impact of maternal factors. However, it does not consider placental factors that may promote injury *in utero*.

The "delayed cesarean section" model uses the combined hypoxic and ischemic insult. In this model, the blood and oxygen supply of the fetus is blocked by occlusion of umbilical vasculature near the term of birth. The seriousness of the consequential brain damage correlates with the timing and length of prenatal ischemia (Robinson *et al*. 2005). Hypoxia-ischemia on gestational day 22 (GD 22) in rabbits (the whole length of gestation is 30 days), or on GD 30 to 35 in guinea pigs (gestation lasts for 65 days) are widely used as models for cerebral palsy, as they cause extensive damage to the cerebral white matter (Coq *et al*. 2016). To reproduce pre-oligodendrocyte damage, ligation of the uterine artery on GD 17-18 is used in rats (the duration of gestation is 22 days) (Robinson *et al*. 2005) that corresponds to intrauterine damage of human fetus at week 23-25 of gravidity (Coq *et al*. 2016). In this model, chronic fetal hypoxia is accompanied by malnutrition of fetus because of the chronic hypoperfusion of placenta. Uterine artery ligation causes growth restriction after birth and leads to loss of oligodendrocytes, astrogliosis in the white matter, microgliosis, neuronal inflammation, and apoptotic cell death. An outcome of these changes is a deceleration of motoric development, that can be recognized up to adulthood (Delcour *et al*. 2011; Robinson *et al*. 2005). Although most of the morphologic changes observed in the prenatal hypoxic-ischemic model in rats are similar to prenatal damage of the human brain, motoric deficiencies of these rats are not identic to defects and spasticity observed in children with cerebral palsy. Rodents are therefore assumed to be more resistant to hypoxia than humans and to need sturdier perinatal brain ischemia to show spastic symptoms (Robinson *et al*. 2005).

Models of Postnatal Insult

Sole hypoxia of differing gravity and timing or anoxia (100% nitrogen) can be induced postnatally, too, in animal hypoxic models studying the impact of hypoxia on brain development. For example, neonatal anoxia on postnatal day 1 led to mitochondrial injury and cellular death in the hippocampus on the next day and to deficits in spatial memory on a postnatal day 60 (Takada *et al*. 2015).

Unilateral postnatal ligation of *arteria carotis* combined with hypoxia is the most widely used model of perinatal hypoxia-ischemia. The first model that combined umbilical cord compression with breathing obstruction used newborn monkeys born in the term (Myers 1972), but in later studies, monkeys were replaced by rats (Vannucci and Vannucci 2005), pigs (Zheng and Wang 2018) or sheep (McClendon *et al*. 2017). The timing of insult also differs depending on the model: Rice-Vanucci model combines carotic artery ligation with exposition to hypoxia on postnatal day 7, which represents damage during the early postnatal period of a preterm baby or of a fetus at weeks 34 to 35 of gestation (Vannucci and Vannucci 2005). This model caused unilateral brain damage and necrosis with consecutive sensorimotor and cognitive deficits in rats. On the other side, hypoxia-ischemia in rats on the postnatal day 2 (that corresponds to a human fetus at gestational week 29-32) aims at proliferation peak of vulnerable pre-myelinated oligodendrocytes (Johnston *et al*. 2005).

However, even these models are not able to adequately mimic human brain damage during the perinatal period. It is to say that most children suffering from cerebral palsy endure the whole-brain damage in the perinatal period. Only a little fraction of them suffers from unilateral damage to the central nervous system seen in these rat models (Robinson *et al*. 2005). Moreover, postnatal hypoxic-ischemic models require surgery and do not take into account the impact of maternal organism and placenta that can also be engaged in mechanisms of fetal brain damage. Lateralization of brain functions (and subsequent site preference of affected animals) makes the interpretation of their behavior in these models even harder.

Hypoxia and Brain

The brain needs the highest amount of oxygen and nutrients of all body organs because it has the highest aerobic metabolism (Koundal *et al*. 2014). The adult CNS is however paradoxically very sensitive to hypoxia, as it does not have enough antioxidant enzymes and has low reserves of substrates needed for anaerobic metabolism (Esih *et al*. 2017). On the other side, developing CNS seems to be more immune to

hypoxia: The elevation of intracellular calcium and the extent of neuronal depolarization after hypoxia or anoxia is much slower in newborns than in adult suspects (Maresová *et al*. 2001).

The impact of hypoxia and ischemia on developing cerebral cells is diverse: from loss of neurons and oligodendrocytes to astrogliosis, changes in cellular differentiation, lowered synapse formation, neurodegeneration, changes in neurotransmitter levels and even to irreversible cellular damage and apoptosis (Robinson *et al*. 2005; Zhang *et al*. 2013). A study of Golan and colleagues showed that transient maternal hypoxia acutely affected neuronal migration in the brain of the fetus. However, they have not observed any acute inflammation or cell death right after the hypoxia, but a significant cellular death 12 days after the hypoxic period that agrees with clinical evidence of late cognitive and behavioral problems following prenatal hypoxia (Golan *et al*. 2009). Authors suppose that this delay may be caused by the model used in the study, as maternal hypoxia is a relatively mild insult to the fetus. Chronic hypoxia also leads to anatomical changes, volume loss, lowered myelination, and ventricle expansion seen in preterm infants but also, interestingly, in patients suffering from schizophrenia (Howell and Pillai 2014). Hypoxia and ischemia were, therefore, proposed as potential animal models of schizophrenia (Hefter *et al*. 2018). In preterm infants, many neuroimaging studies identified significant detraction of structures of cortical and subcortical gray matter area including basal ganglia, thalamus and hippocampus, and a significant neuronal loss in the cerebral cortex (McClendon *et al*. 2014). In a rat model of hypoxia, a significant dilatation of lateral brain chambers was seen, too (Ujhazy *et al*. 2013).

Deterioration in the development of neurons and their connections during the prenatal period can be a cause of behavioral, memory, and cognitive changes later in life. Mild diffuse damage to white matter in preterm children is often associated with behavioral and cognitive impairments, small deficits in proprioception, but never with great motor shortcomings (Delcour *et al*. 2012). Only more significant damage and cell loss caused by severe ischemia can cause motor deterioration, cerebral palsy, and epilepsy.

Corpus Striatum

The striatum is the main input gateway for signals leading to basal ganglia, with medium spiny GABAergic neurons being the main output neurons for it. These neurons are regulated by dopamine and acetylcholine that have contradictory effects in the striatum and can control the release of each other on different levels (Aosaki *et al*. 2010). Activation of muscarinic cholinergic receptors that dominate in striatum controls motoric responses to dopaminergic signalization (Xue *et al*. 2015). Dopamine and acetylcholine together support motor learning, goal- and reward-motivated behavior and habit formation (Guzman *et al*. 2011). Their imbalance can, however, weaken normal reaction selection and lead to pathologic repetitive and compulsive behavior (Crittenden *et al*. 2014). The striatum is very sensitive to hypoxia. Rats subjected to hypoxia (7% oxygen for 3 hours) on GD 13 and 14 had consequently tardive maturation of neuronal cells and heightened neuronal degeneration in cerebral cortex and striatum, as well as coherent behavioral changes, especially defects in motor reactions. These structural changes peaked on postnatal day 20-30 (Dubrovskaya and Zhuravin 2010). In a study on guinea pigs, the offspring of mothers raised in 10,5% oxygen had changes in the striatum, cerebral cortex, and hippocampus up to adolescence (postnatal day 84), with the striatum being most affected (Wang *et al*. 2016).

Hippocampus

Hippocampus is a brain region important for the learning process, new memories' creation, and temporal storage of memory (Abhijit *et al*. 2017). For the stabilization of hippocampal neuroarchitecture, the late embryonic period and the time soon after the birth are crucial (Wang *et al*. 2011). A short high-frequency stimulus induces a long-term strengthening of synaptic transmission in hippocampus known as the long-term potentiation. This potentiation is dependent on NMDA glutaminergic receptors in most synapses (Traynelis *et al*. 2010). Glutamate synapses dominate in the hippocampus (Wang *et al*. 2011) and because of them, the hippocampus is the brain region most vulnerable to hypoxia (Koundal *et al*. 2014). Heightened cholinergic activity in the hippocampus facilitates processing and strengthening of significant external stimuli, but also memory consolidation during later depression of cholinergic activity (Hasselmo

2006). Some authors see a relationship between cholinergic system damage in the forebrain and memory impairment, while spatial memory deterioration is being connected to hippocampal cholinergic system changes. Children, who experienced birth complications, have a reduced mass of hippocampus (Howell and Pillai 2014). In a rodent model, 2 hour-long prenatal hypoxia caused moderate behavioral impairment and cell loss in the hippocampus and cerebral cortex of the offspring in adulthood (Golan *et al*. 2009). Exposure of a developing rat hippocampus to chronic mild hypoxia also leads to cognitive deficits later in life (Raman *et al*. 2005).

Behavioral Consequences of Hypoxia

Hypoxia-induced brain damage has a long-lasting impact on the behavior of the offspring. Children that survived hypoxia-ischemia during labor suffer from learning deterioration, attention deficit hyperactivity disorder (ADHD), disturbances in object recognition and executive functions, such as selective attention, resistance to distraction, planning, behavioral control and decision making (Delcour *et al*. 2012). In animal models, consequences of hypoxia on behavior are similar to symptoms of ADHD. Animals often show hyperactivity, motor and learning deficits, and deterioration in memory, attention, and socialization.

Growth and Early Sensorimotor Development

The growth of embryo and fetus depends on the ability of oxygen and nutrients to pass through the placenta. Lowered oxygen content in the fetal blood significantly reduces its weight and leads to deterioration of its growth *in utero* (Ujhazy *et al*. 2013). Maternal hypoxia causes growth retardation of the rat fetuses (Dubrovskaya and Zhuravin 2010) that can be compensated by a growth spurt during postnatal development (Gonzalez-Rodriguez *et al*. 2014). This compensation is highly significant especially in hypoxic males that can gain weight even above the control level. This weight reduction and following weight gain may be an adaptive reaction of the fetus and newborn to the variable nutrient and oxygen accessibility leading to changes in cellular proliferation.

Various rodent models point out that hypoxia and ischemia have a significant impact on the postnatal development of sensorimotor reflexes of the offspring. These reflexes are inevitable for their adaptation to the new environment. Acute hypoxia (8% oxygen for 4 hours) on GD 17 delayed development of negative geotaxis and righting reflex (Liu *et al*. 2011). Prenatal hypoxia also significantly impaired righting reflex, the coordination of suck and swallow, and motor control of rabbits on postnatal day 1 (Derrick 2004). Chronic hypoxia *in utero* induced by phenytoin led to retarded sensorimotor and reflex development and worsened their performance in the water maze (Dubovický *et al*. 2004). However, another study showed paradox response to hypoxia: hypoxic offspring had longer latency in righting reflex test, but they accomplished the negative geotaxis task even better than controls (Hermans *et al*. 1992). These differences may be caused by hypoxia-induced changes in subcortical areas and cerebellum needed for the righting reflex. On the other hand, negative geotaxis depends mainly on the labyrinth system of the inner ear that is less susceptible to hypoxia.

Motor Functions and Activity

The development of motor functions of hypoxic animals is delayed compared to control animals. In various models of prenatal hypoxic-ischemic injury, rats displayed disturbed motor functions including ataxia, deterioration in motor planning (Robinson *et al*. 2005) and mild spasticity symptoms (Delcour *et al*. 2011, 2012). These deficits were similar to those seen in affected newborns and may be connected to hypoxia-induced disorganization of somatosensory cortex (Coq *et al*. 2016). However, hypoxia alone (7% oxygen for 3 hours on GD 18) was not able to cause morphologic changes in cerebral cortex or striatum, and hypoxic animals differed from controls only in the tonic postural test that requires a significant strength of muscles (Dubrovskaya and Zhuravin 2010).

An open field test revealed the hyperactive behavior of hypoxic rats. However, the duration of this hyperactivity differed between studies: In a rat model of prenatal hypoxia-ischemia on GD 17, the offspring had spontaneous exploratory and motor hyperactivity in the open field test and short-term deficits in object recognition in adulthood (Delcour *et al*. 2012). However, in another study, fetal hypoxia

and anoxia led to hyperactivity in open field only during the postnatal development, while in adulthood, this exploratory activity of the offspring was depressed together with lowered locomotion and higher tendency to freeze (Dubovický *et al*. 2004). Another study also affirms that enhanced motoric activity of hypoxic rats is only temporal and was not observed in adult subjects (Perrin *et al*. 2004). That implies high plasticity of the developing nervous system and its compensatory mechanisms.

Learning

Changes in learning are the most sensitive behavioral markers for detection of the hypoxic impact on the brain. The duration and timing of hypoxia seem to be the factors that contribute most to the seriousness of injury: A study in chicks showed that four days of hypoxia from day 14 of incubation led to their inability to consolidate memory with unchanged learning capacity. However, more serious 8 days–long hypoxia led to an inability to learn new tasks (Camm *et al*. 2005). Anoxia in the neonatal period (Takada *et al*. 2015), hypoxia on GD 14-16 (Gadirova and Agaev 2015), as well as serious postnatal hypobaric hypoxia (Tyulkova *et al*. 2015) impaired spatial learning and working memory of rats. Postnatal monolateral carotid ligation, in combination with hypoxia also led to fewer alterations in T-maze, and damage of learning and memory of the affected rats in the water maze test (Balduini *et al*. 2000).

The changes in learning and memory after hypoxic or ischemic insult usually persist up to adulthood. For example, in a model of postnatal hypobaric hypoxia in rats, the spatial orientation and learning ability in the water maze was deteriorated in their juvenile phase as well as in adulthood (Simonová *et al*. 2003). Chronic intermittent gestational hypoxia in transgenic mice also led to deficits in spatial learning and memory in adulthood (Zhang *et al*. 2013). Deterioration of cognition seen in these studies may be caused by permanent alterations of central noradrenergic transmission induced by hypoxia. Working memory deficit can also be connected to a higher density of inhibitory GABAergic neurons in the prefrontal cortex (Delcour *et al*. 2012).

Emotionality

Prenatal hypoxia changes emotionality of rats. This effect can be seen especially in their increased vocalization when startled, and in anxiety-like behavior in various tests: Prenatal hypoxia (10% O2) for 4 hours on GD 19-20 led to anxiety-like behavior in an elevated plus-maze and light/dark test, seen as less time spent in the open space and lowered exploratory activity of the rat offspring (Sedláčková *et al*. 2014). Prenatal hypoxia and umbilical artery compression also induced anxiety-like behavior in open field test that could be caused by the observed elevation of glutamate receptors in frontal cortex and hippocampus of the affected mice (Howell and Pillai 2014; Sab *et al*. 2013). Animals subjected to asphyxia had more significant grooming behavior and more entries to closed arms of the elevated plus-maze than control animals (Weitzdoerfer *et al*. 2004).

Rats affected by prenatal hypoxia had less social contacts, deterioration of male sexual behavior, smaller cognitive capacity as well as reduced active and passive avoidance reflexes (Dubrovskaya and Zhuravin 2010). Their weaker performance in avoidance tests may be caused by their higher sensorimotor activity, loss of inhibition of spontaneous reactions (resembling children suffering from ADHD) or failure to re-learn and rigidity. Hypoxic animals also had a stronger response to stress-induced hyperthermia, and male rats showed depression-like behavior in a forced-swim test (Sedláčková *et al*. 2014).

Interesting is that some of the earlier studies showed lowered anxiety-like behavior after hypoxia. Elevated plus-maze showed no significant changes in rats after neonatal anoxia (Buwalda *et al*. 1995), while perinatal asphyxia shortened latency to enter open arms and lengthened the time spent in open arms, indicating a lowered anxiety-like behavior in these rats (Hoeger *et al*. 2000). No changes in behavior in open field test or other mazes were found in this study. These opposing results may be caused by different models of insult used in these studies and by the variability in the timing of behavioral tests.

Conclusion

The aim of our work was to discuss some of the newest accessible information about perinatal hypoxia that may be useful also for other researchers. We discussed environmental and placental causes of prenatal hypoxia and various animal models used in research. We also focused on the impact of prenatal hypoxia and possible subsequent ischemia on developing tissues, and its consequences that can last up to adulthood. We briefly summarized possible mechanisms contributing to hypoxic damage of immature organism and paid special attention to the reaction of developing brain and some of its regions to hypoxia and possible behavioral consequences of their damage. We believe that deeper knowledge of reactions following hypoxia and relation between the brain injury and behavioral outcome may be helpful for further research in this field and possible discovery of effective anti-hypoxic therapy.

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Figure 1: Pathways of the hypoxia-induced injury. Hypoxia induces excitatory amino acids release, which may lead to intracellular calcium accumulation and necrosis, but also to apoptosis *via* endonucleases' activation, ROS production, or deleterious effect on mitochondrial functions. ROS production after hypoxia may also be elevated due to inflammation or direct effect of hypoxia on mitochondrial metabolism. Hypoxia stabilizes HIF-1 that elevates expression of pro-apoptotic genes and NO-synthase. NO causes vasodilatation, but also reacts with ROS to produce

reactive nitrogen species. ROS and reactive nitrogen species oxidize proteins and lipids, lead to cellular damage and subsequent apoptosis. HIF-1 – hypoxia-inducible factor 1, NO – nitric oxide, ROS – reactive oxygen species