Chapter

The Role of Vasoregulatory Markers in the Formation of Microcirculatory Changes in Premature Babies with Hypoxic: Ischemic Encephalopathy

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Abstract

Endothelial function plays an important role in the extrauterine adaptation of newborn infants. Endothelium produces different biologically active mediators, which play the central role in physiological and pathological processes and also in the extrauterine adaptation of newborn infants. The imbalance between vasoconstrictive and vasodilatation factors results in impaired cardiovascular adaptation and microcirculation and also brain injury. Microcirculatory disturbances are observed very often in preterm babies, who have a serious risk for perinatal brain injury and further neurodevelopment disabilities. Present chapter presents the pathogenetic role of vascular tone regulators of endothelial genesis in the formation of microcirculatory changes in preterm babies with a high risk of perinatal hypoxic encephalopathy.

Keywords: microcirculation, hypoxic encephalopathy, preterm infants, endothelial function, nitric oxide

1. Introduction

The largest research object of modern perinatology and neonatology is preterm and growth retarded children. Despite the rapid development of perinatal care and the early prevention of many pathologies, worldwide perinatal morbidity and mortality remain high [1–4].

The results of the scientific researches prove that perinatal pathologies play a leading role in the formation of illness, death, disability, social and biological disarray, and different types of neurodevelopmental disorders [5–10]. It is known that birth is a complicated biological process regulated by numerous signal molecules and biologically active substances. The fetal inflammatory response plays a major role in the pathogenesis of premature birth [11]. In addition to prematurity, the hypoxic-ischemic changes in feto-placental system can result in different perinatal pathologies, such as acute intraventricular bleeding, periventricular leukomalation, necrotic enterocolitis, bronchial lung dysplasia, myocardial dysfunction, sepsis, etc. [12–15].

Uteroplacental ischemia and circulatory changes in maternal-fetal system are the main chain in formation intrauterine hypoxia and different perinatal pathologies [16–18]. Previous investigations confirmed the significant role of endothelial function in the formation of different pregnancy pathologies and birth defects [19–22]. The pathogenetic mechanisms of the formation of endothelial dysfunction during uteroplacental ischemia have not yet been investigated. Present chapter explores the role of vascular tone regulators of endothelial genesis in formation of microcirculatory and ischemic changes in preterm infants.

2. The pathophysiology of brain injury in hypoxic: ischemic encephalopathy (HIE)

Adaptation of the child to the extrauterine life significantly depends on the morpho-functional maturity of the organism, and it is more intense and more complicated in preterm babies than mature children [23–25].

The progress of all complicated pathophysiologic processes occurring in the newborn after birth significantly depends on cardiorespiratory adaptation [23, 24]. The changes in the cardiovascular and respiratory functions in the body related to the primarily changes in the microcirculation [25]. Microcirculatory changes are not only clinical symptoms of various pathologies of perinatal period but also one of the major factors that aggravate their course [26, 27].

HIE is one of the most serious birth complications accompanying with microcirculatory changes of different severity [28]. The pathogenesis of vascular changes in preterm infants is quite complicated and involves series of biochemical and molecular reactions (**Figure 1**). Persistent membrane depolarization results in excessive presynaptic glutamate release which follows with a series of cellular changes. The activation of NMDA receptors stimulates profound Ca^{2+} influx, which mediates cascades to cell death. *Primary energy failure* associated with the depletion of oxygen prevents oxidative phosphorylation, and the disrupting Na-K pump activity is

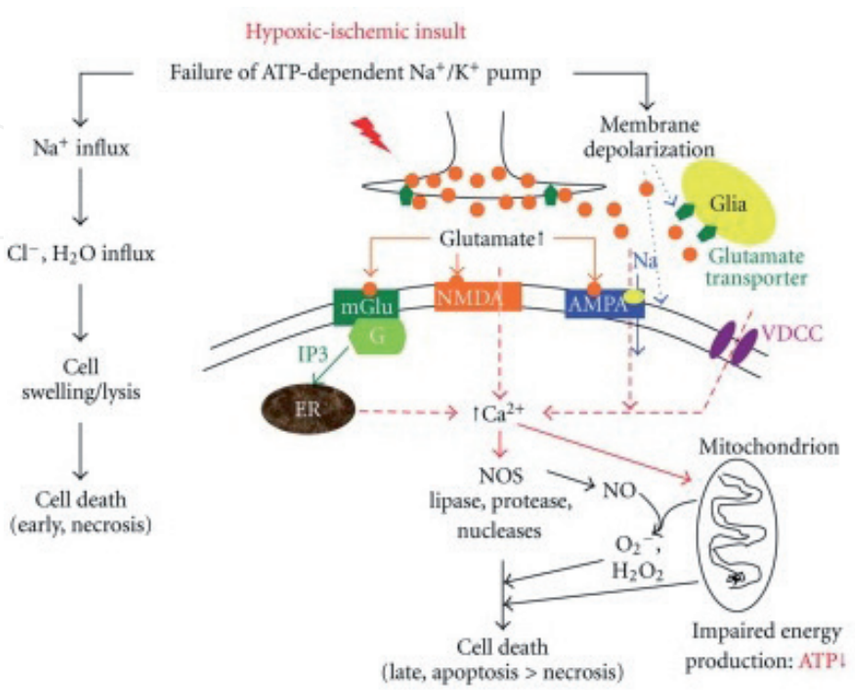

Figure 1.
The pathogenesis of hypoxic-ischemic encephalopathy [33].

followed by anaerobic metabolism with accumulation of lactic acid. With the restoration of blood flow, there is a brief period of normalization of cerebral metabolism called a latent period. The reperfusion is necessary for the recovery and stopping of processes leading to necrotic neuronal injury during the primary phase of injury. However when the brain has not recovered from the initial injury, the reperfusion can simultaneously cause additional (delayed) injury, and mitochondrial dysfunction continues. When cerebral ischemia is more acute and prolonged, especially in the result of accompanying pathological processes (infection, hereditary factors, environmental and other damaging factors), primary injury is followed by secondary injury, which is often characterized by subsequent resulting in more serious neurological and somatic disintegration in development [29]. Secondary injury is often associated with edema of the brain cells. Compensatory restoration of energy reactions is followed by the intracellular edema and by more complex inflammatory response cascade with the presence of free oxygen radicals [30].

Increased amount of free radicals and nitric oxide (NO), increased synthesis of nitric oxide synthase (NOS), activated intercellular adhesion, and apoptosis are the tightly connected chains of this pathological process (10–13). However it is confirmed that endothelial NOS (eNOS) genesis plays very important role in maintaining pulmonary blood flow and preventing pulmonary hypertension. Some experimental studies suggested that *inhibiting NOS could prevent further brain injury* [31]. Selective inhibition of NO of neuronal genesis is more promising in the direction of pathogenetic treatment of HIE in newborn infants [31–33].

The severity of inflammatory processes is correlated with the activation of different mediators, especially cytokines and adhesion molecules. These molecules cause to the migration of leukocytes to the inflammation center and compact adhesion of migrated leukocytes to vascular endothelium [34, 35]. The main stimulus factor for the synthesis of inflammatory mediators is the activation of endothelial cells of the fetus. Thus, endothelial dysfunction is the main factor that stimulates intracellular and vascular adhesion and leads to the activation of fetal leukocytes [36, 37].

There is much to be investigated how the inflammatory response to hypoxia is regulated and the complete role of different mediators as well as vasoregulatory, anti-inflammatory, and apoptosis molecules under physiological and pathological conditions is unknown. The goal of this chapter is to present the results of recent investigations about the role of vasoregulatory markers in the formation of microcirculatory disorders in hypoxic-ischemic encephalopathy of preterm infants.

3. Endothelial dysfunction and microcirculatory disorders in HIE of preterm infants

Several clinical and experimental studies confirmed the role of endothelial dysfunction in the pathogenesis of hypoxic-ischemic brain injury. The prospective clinical trial of Azerbaijan Medical University Neonatology group (ACTRN12612000342819) determined that the eNOS activity is declined in the background of increased NO concentrations depending on the severity of HIE [38].

The aim of the same study was also to study of the peripheral blood concentrations of vasoregulatory mediators of endothelial genesis in the pathogenesis of microcirculatory changes in newborn children with the birth asphyxia. It investigated 240 preterm infants with a high risk of HIE during early neonatal period. The main groups of children were classified into four groups depending on the degree of the microcirculation changes. The first group included preterm infants without microcirculatory changes of the body. The children with mild-degree microcirculatory disorders (continued less than 1 day and self-regenerating

peroral and acrocyanosis, capillary refilling time duration less than 3 s) were included in the second group. The third group consisted of children with moderate microcirculatory disorders (such as peroral and acrocyanosis, marbling of the skin, capillary refilling time up to 7 s and continuing from 1 day up to 3 days). The fourth group consisted of children with severe microcirculatory disorders (acute peroral and acrocyanosis, marbling of the skin continuing more than 3 days, capillary refilling time with the duration of more than 7 s and continuing more than 3 days). The parameters were compared with the data of 2 control groups, which consisted of infants without perinatal and neonatal pathologies: 22 healthy preterm infants were included in control 1 and 30 healthy term infants in control 2.

Depending on the magnitude of the microcirculatory defects, the levels of vasoregulatory markers included in the study is shown in **Table 1**. The statistically significant reduction in eNOS activity in the first few days of life is noticeable, depending on the degree of severity of the microcirculatory disturbances. However toward the end of the early neonatal period in mild and moderate group children, eNOS concentrations significantly increased compared with children with severe microcirculatory changes and control groups.

As shown in **Table 1**, during severe microcirculation defects, NO synthesis of vascular endothelium remains at very low levels. In contrast, NO levels in the early days of the neonatal period were noted to significantly increase in infants with severe microcirculatory disturbances, and in the dynamics of the neonatal period, regardless of the microcirculatory changes severity, it is observed the increase of NO concentrations. At the same time, vasoconstrictor endothelin-1 levels rise during mild and moderate grades of microcirculation changes, while in infants with severe changes, it is reduced. This also proves once again that severe microcirculation disturbances lead to a violation of blood supply both in peripheral and vital organs during acute brain damage. We suggest that the lack of adequate levels of endothelin-1 synthesis, which is vasoconstrictor mediator of vascular endothelium in addition to decreased endothelial NOS activity, becomes one of the main points in the pathophysiology of HIE in preterm infants.

The follow-up results of these children included in this study identified significant relationships between peripheral endothelial vasoregulatory markers in the perinatal period and the formation of developmental disorders at an early age [39]. It was found that, in the presence of high concentrations of NO, early eNOS activity was insufficient in infants with moderate-to-severe neurodevelopmental disorders compared to neonates with mild neurologic changes or without evidence of neurological impairment (**Table 2**). These findings suggest that depressed eNOS activity and increased non-endothelial NO synthesis play also important roles in the formation of developmental impairments.

It is known that there is a disturbance of vasoregulation in the pathogenesis of various pathologies of the HIE and prenatal period [40–42]. Depending on the complexity of the pathological process and the degree of morphologic and functional immaturity of the body, hypoxic-ischemic lesions can lead to generalized system damage from mild to generalized severe dysfunctions and changes [43–47]. Acceleration of blood supply to vital organs during HIE is accompanied by peripheral vasospasm. However, the depletion of vascular tone's regulating mechanisms during the severe and long-lasting processes leads to the tissue hypoxia and acidosis [40–47]. This often leads to changes in vital organs, especially in brain tissue whose results are with changes that cannot be restored.

It is considered that statistically significant increase of NO levels in peripheral blood circulation during severe hypoxic changes is due to the exhaustion of endothelial NOS sources and the activation of non-endothelial NO synthesis sources.

		N	Mean	SE	p<0,05	95% CI		Min	Max
eNOS 1-3rd day	none	20	10,28	1,24	1,2,3,#, ^	7,67	12,89	0,30	21,20
	mild	28	6,65	1,12	0,3,#^	4,35	8,96	0,00	22,20
	moderate	28	5,84	0,91	0,#,^	3,97	7,72	0,04	13,50
	severe	18	3,10	0,79	0	1,43	4,77	0,30	13,50
	control 1	22	2,11	0,09		1,92	2,31	1,50	2,90
	control 2	30	1,98	0,06		1,84	2,12	1,50	2,70
eNOS 7-10th day	none	4	2,56	0,86	^	0,18	5,31	0,06	4,00
	mild	17	5,29	1,49	#,^	2,11	8,46	0,06	24,40
	moderate	25	5,23	1,17		2,79	7,66	0,06	24,40
	severe	11	2,14	0,27		1,53	2,75	0,70	3,70
	control 1	22	1,80	0,06		1,67	1,93	1,30	2,30
	control 2	30	1,33	0,04		1,23	1,43	0,90	2,20
NO 1-3rd day	none	24	29,47	2,24	2,3	24,82	34,12	16,00	53,40
	mild	49	36,41	1,05	2,3,^	34,29	38,52	16,00	49,20
	moderate	58	48,46	2,89	0,1,3,#, ^	42,67	54,25	16,00	99,40
	severe	24	70,40	5,56	0,1,2,#, ^	58,88	81,91	22,00	99,40
	control 1	22	27,95	0,66		26,57	29,33	23,00	35,00
	control 2	30	23,20	0,57		22,02	24,37	16,00	31,00
NO 7-10th day	none	20	35,73	3,49	^	28,42	43,03	0,80	50,80
	mild	50	27,05	2,28	2,^	22,46	31,63	0,80	50,80
	moderate	39	36,12	2,44	1,5,^	31,18	41,07	0,80	50,80
	severe	6	36,06	4,67	^	24,05	48,08	25,60	50,80
	control 1	22	25,36	0,77		23,74	26,97	16,00	32,00
	control 2	30	17,43	0,63		16,13	18,72	10,00	23,00
ET-1 1-3rd day	none	29	3,23	0,65	3,^	1,89	4,56	0,18	12,18
	mild	49	4,58	0,55	^	3,47	5,69	0,21	13,02
	moderate	58	4,21	0,57	1	3,06	5,36	0,21	13,02
	severe	29	2,32	0,49		1,32	3,33	0,63	13,02
	control 1	22	2,83	0,09		2,63	3,02	1,85	3,90
	control 2	30	1,85	0,05		1,73	1,97	1,10	2,40
ET-1 7-10th day	none	22	2,16	0,25		1,63	2,70	0,84	6,49
	mild	38	2,69	0,35		1,98	3,41	0,42	9,93
	moderate	45	3,43	0,38		2,66	4,21	1,05	9,93
	severe	24	2,90	0,32		2,23	3,57	0,42	7,36
	control 1	22	1,88	0,05		1,77	2,00	1,40	2,30
	control 2	30	1,53	0,07		1,37	1,68	0,90	2,30

Table 1.
The level of vasoregulatory indicators in microcirculatory disturbances in children with HIE risk (p<0,05 in comparison with children with 0-none of, 1- mild, 2-moderate, 3-severe microcirculatory changes, and with # - Control 1, ^ - Control 2 infants).

It is likely that in high endothelin-1 levels in children, mild and moderate changes are likely to compensate for an increase in peripheral vein tone and vital organs to maintain normal blood circulation. Reduced vasoconstrictor endothelium-1 levels in children with severe HIE symptoms are likely to be associated with decreased vascular tone and tissue hypoperfusion. In conclusion, the changes of capillary blood circulation in the result of endothelial dysfunction have the main role in the pathogenesis of hypoxic-ischemic inflammation in preterm infants.

Variables	Groups	N	Mean±SD	Minimum	Maximum	[a]p value
eNOS, IU/ml, day 1-3	1st group	8	4,65±1,67	2,50	7,60	1-c p<0,01 2-c p<0,01 3-c p<0,01
	2nd group	20	7,71±3,55	3,20	15,00	
	3rd group	14	6,71±3,83	2,80	15,00	
	control group	20	2,09±0,63	0,70	3,20	
eNOS, IU/ml, day 7-10	1st group	8	1,37±0,43	0,70	1,90	1-2 p<0,05 1-3 p<0,05 2-3 p<0,05 2-c p<0,05 3-c p<0,01
	2nd group	20	2,64±1,01	0,60	4,10	
	3rd group	14	7,57±3,27	3,90	14,00	
	control group	20	1,85±0,74	0,50	3,20	
NO, mmol/l, day 1-3	1st group	8	47,50±17,51	23,00	72,00	1-c p<0,05 2-c p<0,01 3-c p<0,01
	2nd group	20	45,60±12,39	23,00	72,00	
	3rd group	14	42,85±13,40	19,00	68,00	
	control group	20	25,00±7,72	16,00	41,00	
NO, mmol/l, day 7-10	1st group	8	69,37±13,74	45,00	87,00	1-2 p<0,05 2-3 p<0,05 1-c p<0,01 2-c p<0,05 3-c p<0,01
	2nd group	20	65,00±31,04	17,00	108,00	
	3rd group	14	43,57±14,71	19,00	68,00	
	control group	20	26,50±7,97	16,00	41,00	
Endothelin-1, pg/ml, day 1-3	1st group	8	5,71±2,60	3,20	7,20	1-2 p<0,05 1-c p<0,01 2-c p<0,01 3-c p<0,01
	2nd group	20	4,43±1,55	1,30	6,70	
	3rd group	14	5,70±1,73	3,20	7,90	
	control group	20	2,71±0,56	1,60	3,90	
Endothelin-1, pg/ml, day 7-10	1st group	8	3,92±1,08	2,60	5,60	1-2 p<0,05 2-3 p<0,05 1-c p<0,01 2-c p<0,01 3-c p<0,01
	2nd group	20	5,91±1,61	3,20	8,60	
	3rd group	14	4,02±0,93	2,60	5,60	
	control group	20	1,82±0,69	,90	3,90	

Table 2.
Blood concentrations of vasoregulatory markers in the early neonatal period by study groups. 1st group: HIE infants diagnosed with moderate-to-severe neurodevelopmental disorders or cerebral palsy; 2nd group: HIE infants with mild neurologic changes at an early age; 3rd group: HIE infants without evidence of neurological impairment in the post-neonatal period; control group: healthy preterm infants. [a]p<0,05 is considered statistically significant between main groups (1-2, 1-3, 2-3), and between main and control groups (1-c, 2-c, 3-c).

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Conflict of interest

The authors declare no conflict of interests.

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