Effect of Acute Progestational Hypoxia on the Content of Biogenic Amines in the Brain of Albino Rat Pups: Peptide Correction

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We studied the effect of exposure to acute hypobaric hypoxia in the progestational period on the content of biogenic amines in the brainstem and cerebral cortex in rat pups of different age. The possibility of correcting hypoxia-induced changes with regulatory peptides was evaluated. We found that early antenatal hypoxia disturbs maturation of catecholaminergic systems in the brain. It should be emphasized that the differences from the control varied depending on the age of rat pups. Single intranasal administration of Semax heptapeptides and β-casomorphine-7 to pregnant females prevented changes in the content of biogenic amines in CNS of the offspring during postnatal ontogeny.

Key Words: *antenatal hypoxia; newborn rat pups; biogenic amines; regulatory peptides*

Asphyxia and hypoxic traumatic injury of the brain are the major causes of fetal death in the antenatal period. Moreover, these disturbances determine further development of children and the incidence of mental and physical disability [1,3]. Antenatal damage to the brain plays a role in the pathogenesis of cerebral palsy with ataxia, epilepsy, and minimal brain dysfunction and constitutes more than 60% diseases of the nervous system in children [7]. The influence of acute and chronic fetal hypoxia on the state of CNS is of particular interest in this respect.

Postnatal pathology in the CNS caused by antenatal hypoxia can be determined by imbalance in biogenic amines of the brain. Experiments of L. D. White and E. E. Lawson showed that chronic antenatal hypoxia at the late stage of embryogenesis affects catecholamine synthesis in rat pups [10].

Peptide complexes (constellations) consisting of potentially protective components hold promise for the correction of posthypoxic changes [4]. Combination treatment with peptides not only extends the spectrum of their actions, but also produces new effects.

Here we studied the effect of acute progestational (preimplantation) hypoxia modeled in female rats on days 4-5 of pregnancy on the content of biogenic amines dopamine, norepinephrine, and serotonin in the brainstem and cerebral cortex of their offspring. We also evaluated the possibility of preventing the negative effects of hypoxia with the peptide complex.

MATERIALS AND METHODS

Acute hypobaric hypoxia (AHH) in female albino rats was modeled in an altitude chamber on days 4-5 of pregnancy.

AHH was modeled at 145 mm Hg, which corresponded to an altitude of 11,500 m above sea level

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TABLE 1. Age-Related Changes in the Content of Biogenic Amines in Cerebral Cortex and Brainstem of Rat Pups (μg/g, *M*±*m*)

Brain structure		Age, days			
		15 (*n*=18)	22 (*n*=23)	36 (*n*=17)	57 (*n*=16)
Cerebral cortex	dopamine	0.27±0.05	0.29±0.07	0.39±0.03*	0.44±0.07*
	norepinephrine	0.12±0.03	0.19±0.04	0.25±0.03*	0.28±0.05*
	serotonin	0.20±0.03	0.31±0.03	0.35±0.02*	0.37±0.01*
Brainstem	dopamine	0.68±0.08	0.48±0.15	0.99±0.02*	0.91±0.02*
	norepinephrine	0.22±0.08	0.31±0.05	0.42±0.06*	0.47±0.07*
	serotonin	0.37±0.03	0.52±0.07	0.61±0.07*	0.72±0.10*

Note. *p<0.05 compared to day 15. Here and in Table 2: *n*, number of animals.

(the ascent took 1 min) [1]. Physiological saline (PS) or peptide constellation (PC) was administered intranasally 15 min before hypoxia. Control rats received an equivalent volume of PS or PC, but were not subjected to hypoxia. PC contained heptapeptides Semax (0.1 mg/kg) and β-casomorphine-7 (0.1 mg/kg). Published data show that Semax possesses antihypoxic and nootropic properties [5], while β-casomorphine-7 produces a neurotropic effect against the background of pharmacological changes in the brain [2]. Thus, these regulatory peptides can prevent or abolish the negative consequences produced by acute hypoxia.

The content of biogenic amines in the brainstem and cerebral cortex of newborn male and female rat pups was measured by fluorescence assay. The concentrations of dopamine and norepinephrine were estimated by the method of G. Metcol. The amount of serotonin was determined as described by E. P. Miller and R. P. Maike. The specimens were taken on days 15, 22, 36, and 57 of life.

The data were processed using Statist and Excel softwares. The differences were evaluated by Student's *t* test.

RESULTS

The contents of dopamine, norepinephrine, and serotonin in the cortex and concentrations of norepinephrine and serotonin in the brainstem progressively increased with age during the normal course of postnatal ontogeny (Table 1). On day 36 of life the content of biogenic amines in the cerebral cortex and brainstem was much higher than in 15-day-old animals. The concentration of biogenic amines in these structures remained high for at least 3 weeks (up to the 57th day of postnatal development).

The content of biogenic amines markedly changed in brain structures of rats subjected to acute hypoxia in the early prenatal period. It should be emphasized that these changes depended on the age of rat pups. The content of biogenic amines in the cortex and brainstem increased on day 15, but decreased on day 22 of life. At later stages of postnatal development (days 36-57) the concentration of biogenic amines increased and decreased only in the brainstem (Table 2).

Single intranasal administration of PC to pregnant females 15 min before AHH abolished changes in the

TABLE 2. Effect of PC on Changes in the Content of Biogenic Amines in Brainstem and Cerebral Cortex of Rat Pups Induced by Acute Progestational Hypoxia (% of Control, *M*±*m*)

Age, days		Cerebral cortex			Brainstem		
		dopamine	norepinephrine	serotonin	dopamine	norepinephrine	serotonin
15	PS+AHH (*n*=10)	108±11	236±36*	100±15	130±11**	143±14**	130±11**
	PC+AHH (*n*=7)	92±9	129±27	103±6	129±29	117±18	129±29
22	PS+AHH (*n*=12)	43±7*	45±10*	85±6**	81±3*	87±13	81±7**
	PC+AHH (*n*=12)	90±18	71±15	94±10	101±9	102±8	115±12
36	PS+AHH (*n*=12)	124±7	123±12	92±2	145±12**	193±6**	74.6±6.0**
	PC+AHH (*n*=16)	169±21**	128±16	98±4	116±5	100±10	115±10
57	PS+AHH (*n*=18)	108±10	103±10	103±12	95±8	116±12	162±20**
	PC+AHH (*n*=14)	102±7	101±11	104±11	117±14	100±13	133±18

Note. *p<0.01 and **p<0.05 compared to the control.

content of biogenic amines in the brainstem and cerebral cortex of their offspring (Table 2).

The protective effect of PC was probably associated with prevention or attenuation of pathological changes in the course of pregnancy and embryogenesis produced by progestational hypoxia. It can be hypothesized that this effect of PC is related to antihypoxic and anxiolytic properties of its components Semax and β-casomorphine-7. Moreover, the route of administration ensured the direct effect of PC on CNS [6,8].

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