Effect of Antenatal Hypoxia on Age-Specific Dynamics of ECG Parameters and Content of Biogenic Amines in the Central Nervous System

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We studied the effect of acute antenatal hypoxia during the stages of progestation and early organogenesis on some ECG parameters and level of biogenic amines in brain structures in rats. The effect of acute hypoxic exposure during the organogenesis period on the studied parameters was more pronounced than the effect of acute hypoxic exposure during the progestation period. The shift of the autonomic balance towards the sympathetic regulation of cardiac activity is linked with increased content of biogenic amines in the brain stem and cortical structures.

Key Words: *antenatal hypoxia; electrocardiogram; autonomic balance; biogenic amines*

Changes in the cardiovascular function of the fetus exposed to antenatal hypoxia often lead to the development of severe diseases in newborns and to high risk of cardiovascular disease in adults. The effects of antenatal hypoxia on the progeny can be immediate and delayed, often irreversible, manifesting, for example, by changed balance of autonomic regulation [4,8]. The autonomic balance directly depends on the biogenic amine system in the CNS [1,3]. Changes in the content of norpinephrine (NE), dopamine (DA), and serotonin (5-HT) in the cortex and brain stem are essential for the peripheral component of the autonomic nervous system and hence, for autonomic regulation of the effector organs, including the heart.

Analysis of some ECG parameters, in particular the length of *RR* interval and mode amplitude (AMo), under conditions of spontaneous behavior of animals in a chronic experiment is widely used for evaluation of the balance of autonomic regulation. These parameters allow indirect evaluation of the status of various components of the autonomic regulation of cardiac activity, autonomic balance, status of the subcortical cardiovascular center, and individual components of the regulatory mechanisms [2]. Evaluation of age-specific dynamics of these parameters reflecting maturation of the autonomic regulation of the heart in rats during the early postnatal period in health and after antenatal hypoxia is of particular interest.

Previous studies revealed differences in the resistance of female rats to acute hypoxia during different periods of gestation. The highest sensitivity to acute hypobaric hypoxia was observed during the progestation period (days 3-5 of pregnancy) and during the early organogenesis period (days 9-10 of pregnancy) [7].

Here we evaluated the effect of acute hypobaric hypoxic exposure during these periods on the

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development of the autonomic balance by changes in age-specific dynamics of the main ECG parameters and compared the data with the effects of acute hypoxia on the content of biogenic amines in CNS.

MATERIALS AND METHODS

The study was carried out on 436 outbred albino rat pups of both sexes, the progeny of 68 females. The females were exposed to acute hypoxia on days 4-5 and 9-10 of pregnancy. The day on which spermatozoa were detected in vaginal smears was considered as the 1st day of gestation. Days 4-5 of pregnancy correspond to the stage of transition of a 16-32-cell embryo into the uterus (progestation stage), days 9-10 are the initial stage of organogenesis. Acute hypobaric hypoxia was simulated in a 3.3-liter pressure chamber at a "height" corresponding to 11,500 m above sea level ("elevation rate" 200 m/sec) with partial oxygen content of 4-5% [5,6,9]. Pregnant females were left under conditions of acute hypoxia until respiration arrest; the mean time was 152.0±9.1 sec. The progeny of females not exposed to hypoxia served as the control.

The main ECG parameters were analyzed on days 22, 36, and 56 of life in control (n=189) and experimental (n=199) rat pups under conditions of spontaneous behavior in a box with holes. One day before recording, the electrodes for ECG monitoring in a standard lead were subcutaneously implanted to animals under nembutal (30 mg/kg intraperitoneally) narcosis. ECG was recorded for 2 min as a curve presenting the dynamics of an analog signal digitalized at a frequency of 500 Hz using ISCOUP software.

The data were statistically processed using SPIKE-C3 and INTERVALS 1.02 software, allowing estimation of the mean *RR* intervals and AMo values (percentage of the most incident *RR* interval). Changes in these parameters in experimental groups were presented in percent of the values in the control.

The levels of biogenic amines (DA, NE, 5-HT) in the brain stem and cortex of rat pups of both sexes (n=48) were measured on day 56 of life by the fluorescent analysis.

RESULTS

The length of *RR* interval increased and the AMo value decreased significantly in control pups of both sexes from day 22 through 36 of the postnatal period (Fig. 1, *a*, *b*), which indirectly indicates increased involvement of the parasympathetic component into the regulation of the chronotropic parameters of cardiac activity [2].

From day 36 through 56 of life, further lengthening of the *RR* interval was observed only in male progeny; AMo values did not change during this period in the progeny of both sexes.

Hence, a stable level of the chronotropic parameter was attained by day 36 of life in females, while in males it was not attained even in mature rats (day 56 of life).

Age-specific dynamics of ECG parameters in males and females exposed to hypoxia *in utero* during the progestation period was the same as in the control group: no appreciable deviations of the studied parameters from the control values for each age, taken for 100% (Fig. 2, *a*, *b*).

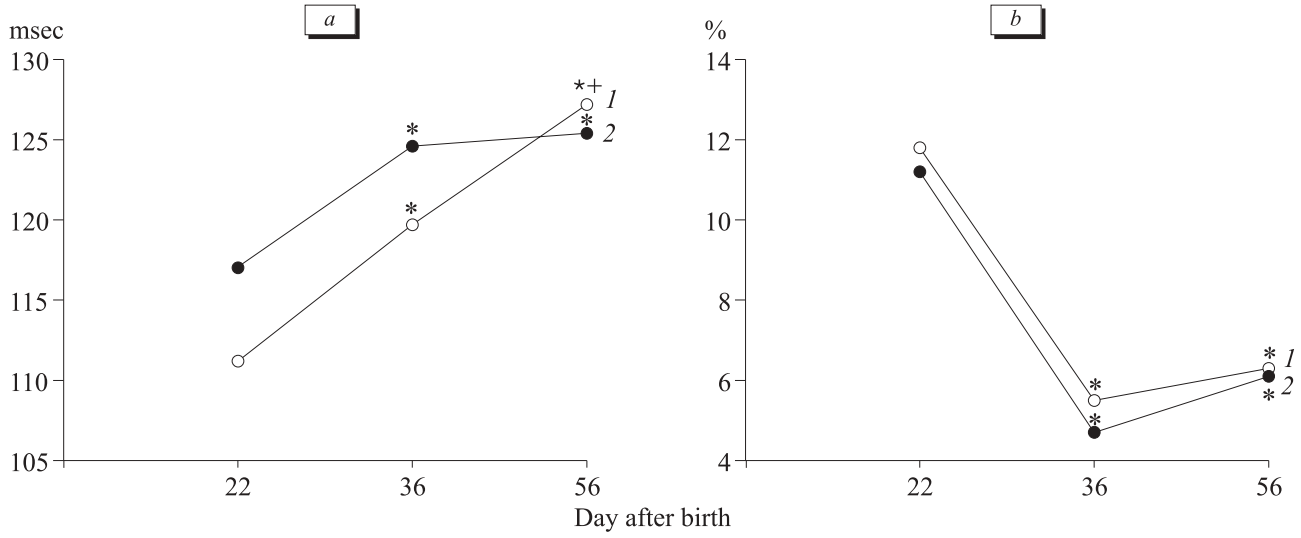

Fig. 1. Mean values of *RR* interval (*a*) and AMo (*b*) in control animals. Here and in Fig. 2: *1*) males; *2*) females. $p<0.05$ compared to: *day 22, +day 36.

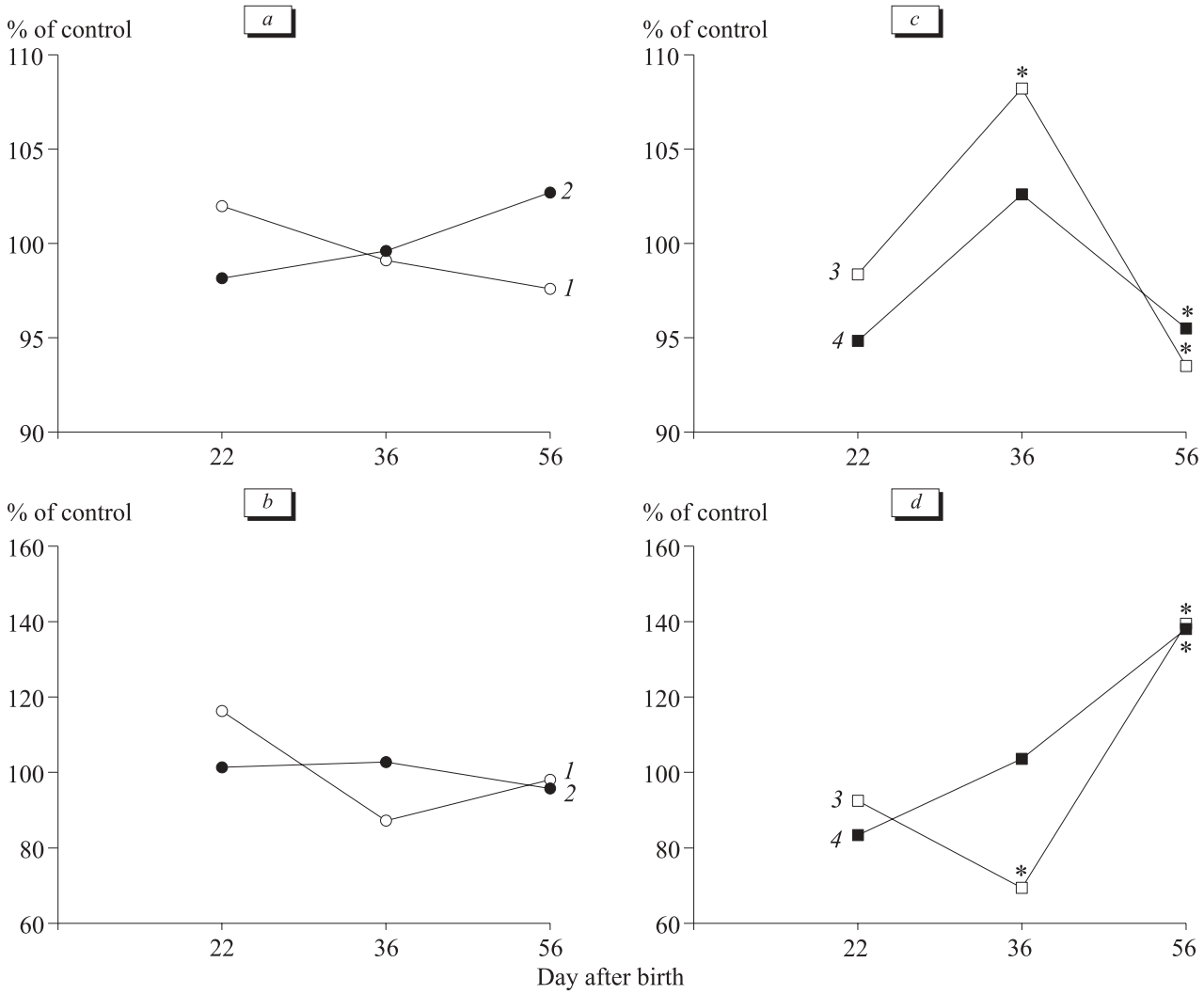

Fig. 2. Effects of antenatal hypoxic exposure during the progestation (*a*, *b*) and early organogenesis periods (*c*, *d*) on ECG parameters: mean *RR* interval (*a*, *c*) and AMo values (*b*, *d*). *$p<0.05$ compared to the control.

Antenatal hypoxia during the early organogenesis led to changes in age-specific dynamics of both ECG parameters: in contrast to the control, the length of the *RR* interval decreased significantly by the age of 56 days in males and females, which correlated with significant increase of AMo value. Significant differences from the control were also observed for the absolute values of the studied parameters. In males, these differences appeared as early as at the age of 36 days and manifested by a

TABLE 1. Effects of Antenatal Hypoxic Exposure during the Progestation and Early Organogenesis Periods on the Content of Biogenic Amines in the Cerebral Cortex and Brain Stem of Rats on Day 56 of Life (% of control; *M*±*m*)

Parameter	Brain stem			Hemispheric cortex		
	NE	DA	5-HT	NE	DA	5-HT
Hypoxia during progestation period						
males (*n*=8)	104±14	89±16	188±26*	105±13	95±17	95±2
females (*n*=8)	105±11	97±8	118±4	99±7	113±14	116±5
Hypoxia during organogenesis period						
males (*n*=17)	139±11*+	132±15*+	119±16+	138±10*+	143±9*+	91±7
females (*n*=15)	102±9	132±19*+	135±21*+	127±28+	92±16	115±11

significant prolongation of *RR* interval and a decrease of AMo, indirectly indicating a shift of the autonomic balance towards activation of the parasympathetic regulation contour. However, at the age of 56 days the length of the *RR* interval decreased significantly in experimental males and females, while AMo increased; in other words, the autonomic balance shifted significantly towards the sympathetic component.

Hence, the effect of hypoxic exposure during the early organogenesis period manifested in intensification of the sympathetic contour of regulation of the chronotropic parameter in mature animals of both sexes.

This shift can be determined by shifted balance of bioamines in the CNS. Antenatal hypoxia caused changes in the content of biogenic amines in the CNS (Table 1). These changes were most pronounced in animals exposed to hypoxia during the early organogenesis stage and were more expressed in male progeny: hypoxic exposure during the progestation period significantly increased only 5-HT content in the brain stem, while exposure during the early organogenesis period increased the content of NE and DA in the brain stem and in the cortex. In females hypoxic exposure during the early organogenesis period increased the levels of 5-HT and DA in the brain stem. It is noteworthy that the levels of biogenic amines in the CNS were higher in almost all cases after hypoxic exposure during the early organogenesis stage in comparison with the control and even in comparison with the values in animals exposed to hypoxia during the progestation period, except the level of 5-HT in the brain stem.

Hence, our data suggest that the main cause of the shift in the balance of autonomic regulation of the chronotropic parameters of cardiac activity towards the sympathetic component after antenatal hypoxia of the early organogenesis period is high level of biogenic amines in the brain stem and cortical structures.

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