EXPERIMENTAL BIOLOGY

EFFECT OF BETA-ADRENOMIMETICS ON FORMATION OF BLOOD PRESSURE AND HEART RATE RHYTHMS

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The chronobiological approach has won for itself increasing popularity both in experimental physiology and in clinical medicine. By the use of this approach much progress has been made in the study of the pathogenesis of various diseases, their treatment, and prediction of their development and outcome [9, 10]. The international program of chronobiologic research, with the name "Womb-to-Tomb," involves all age periods from intrauterine development to old age. The results described in this paper were obtained within the context of this program. They constitute three interconnected fragments, aimed at studying ability to predict essential hypertension in the early stages of life and the effect of genetic and exogenous factors acting in the antenatal period on its development.

The aim of the first fragment was to study characteristics of circennial modulation of ultradian rhythms of systolic and diastolic arterial blood pressure (SSP and DBP) and the heart rate (HR) in premature infants, with the aim of seeking criteria that can be used in the early postnatal period to assess the risk of development of hypertension in later life.

The problem was tackled on the basis of the results of previous investigations [10], in which the so-called "Chronome Prematurity" was found in premature newborn infants, i.e., it was shown that ultradian, circadian, circaseptan, and circennial rhythms in some children may be expressed immediately after birth. This has been observed in cases when the family history included hypertension and/or other cardiovascular diseases.

It has been suggested that similar differences between chronomes may also be found at earlier stages of development, namely in premature infants born between 26 and 37 weeks. In that case, a difference can be found in the relationship between the ultradian and circennial components of the rhythm spectrum in premature infants with high and low risk of cardiovascular diseases. The aim of this investigation was accordingly to discover whether the circennial rhythm leaves its mark on the 3-hourly rhythm, synchronized mainly with feeding, and whether such modulation depends on the degree of risk of hypertension and of cardiovascular diseases.

The aim of the second fragment was to study the development of the temporal structure of adrenocortical function as a possible endocrine mechanism linked with the appearance of features characterizing the risk of development of hypertension in later life during the neonatal period.

In children even before the age of puberty, a circadian rhythm of adrenal hormone production is found, and may be observed both by an indirect method of counting the number of eosinophils in the blood [11] and by a direct method, by measuring 11-hydroxycorticosteroids [5, 13]. In view of a communication describing involution of the adrenals after birth [14], it was very important to discover whether the cyclic pattern of production of adrenal hormones, which is lost soon after birth and reappears later, may be present in premature infants [5, 11, 13]. Since the risk of development of hypertension, linked with the family history, appears soon after birth [10], it can be tentatively suggested that adrenal mechanisms, whose influence is strengthened before birth [12], are involved in this process.

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TABLE 1. Amplitude of Circennial Fluctuations of Parameters of 3-Hourly Rhythm in Premature Infants

	Amplitude				Mesor			
Group	F −M−	F +M−	F −M+	F +M+	F −M−	F +M−	F −M+	F+M+
n	139	58	85	12	139	58	85	12
SBP	0,498	7,708	0,809	7,872	1,421	6,910	2,339	7,786
p	NS	<0,001	NS	<0,01	NS	<0,001	<0,01	<0,05
DBP	0,071	5,259	0,594	3,903	0,956	5,051	1,557	5,448
p	NS	<0,001	NS	<0,05	NS	<0,001	NS	<0,05
HR	2,293	0,786	2,387	5,537	4,709	13,142	6,169	2,439
p	<0,01	NS	NS	NS	<0,05	<0,001	<0,05	NS

*Fenoterol; **ritodrine.

The aim of the third fragment was to obtain information about all circadian rhythms of SBP, DBP, and HR in clinically healthy children aged 11-14 years in order to compare their characteristics with those of children subjected and not subjected to the action of beta-adrenomimetics in the antenatal period.

EXPERIMENTAL METHOD

Chronograms of SBP, DBP, and HR of premature infants with a body weight of 650-2550 g at birth were recorded and analyzed as described previously [1]. The resulting (transverse) series of data (mesor and amplitude of 3-hourly rhythms), correlated with the date of investigation, were approximated by a sinusoid with a period of 365.25 days. Concentrations of Na^+ and K^+ and also of 11-HCS were examined in each cycle of urine collected at intervals of 3 h for 24 h from 21 premature infants aged 2-10 weeks. By means of a portable monitor (model ABPM-630, COLIN Medical Instruments, Japan) SBP, DBP, and HR were recorded for 48 h at intervals of 15 min in 14 boys and five girls aged 11-13 years, with the normal rhythm of sleep and waking. In the antenatal period, nine of the 19 children tested had received various doses (0.05-1.323 g) of beta-adrenomimetics (partusisten,* ritodrine, or Yutopar**), which pregnant women had been given to prevent premature labor. In the remaining 10 cases, although the course of pregnancy had been the same, no beta-adrenomimetics had been given. Analysis of the data of the 2nd and 3rd fragments of the work was done by methods of individual and population cosinor analysis [6].

EXPERIMENTAL RESULTS

Plotting the histogram of the optimal periods of SBP and DBP showed that for premature infants a 3-hourly rhythm is the most characteristic. This served as the basis for its choice for the analysis of circennial modulation, the results of which are given in Table 1.

Circennial modulation of the amplitude and mesor of the 3-hourly rhythm of BP was observed mainly in premature infants with a family history of hypertension in the paternal line (F+M−) or with a combination of a history of hypertension in both paternal and maternal lines (F+M+). Circennial modulation was found for the mesor of the 3-hourly SB rhythm, but was not found for its amplitude in children with a positive family history for hypertension in the mother (F−M+) and it was absent in children with a negative family history (F−M−). As regards HR, statistically significant circennial modulation of the amplitude of the ultradian fluctuations was found only in children with a negative family history for hypertension. Circennial modulation of the mesor of ultradian fluctuations of HR was significant in all groups, except a small group of children with a positive history in both paternal and maternal lines. The data thus indicate not only that a chronobiological approach can be used to distinguish children with high and low risk of development of cardiovascular diseases later in the early postnatal period, but also the genetic nature of differences in the chronome.

Examination of chronograms of renal excretion of electrolytes and 11-HCS revealed 24-hourly fluctuations around a mean value, which were more "regular" for Na^+ and K^+ than for 11-HCS excretion (Table 2).

TABLE 2. Amplitude and Acrophase of Circadian Rhythms of Excretion of Na^+, K^+, and 11-HCS with the Urine of Premature Infants

Parameter in urine	Amplitude	Acrophase	
		ч	p
Na+	30.90 (% of mean)	13.03	0.011
K+	30.15 (% of mean)	10.60	0,085
Na+/K+	2.22	13.20	0.494
11-HCS	0.04 (μg)	23.93	0.671
* »	0.86 (μg)	5.39	0.385

Legend. Asterisk indicates individual data.

TABLE 3. Parameters of 24-Hourly Rhythm in Children Aged 11-13 Years

Group	Beta-adrenomimetic	Control	p
SBP			
Mesor	112.2±4.6	106.9±5.4	<0,05
Amplitude	14.4±4.1	12.2±2.6	NS
Acrophase	14.78±0.68	14.37±0.90	NS
DBP			
Mesor	64.3±3,1	61.0±2.9	<0,05
Amplitude	10.7±2.7	9.2±2.0	NS
Acrophase	14.73±0.59	14.10±0.89	NS
HR			
Mesor	78.9±8.0	80.0±7.3	NS
Amplitude	13.6±3.3	13.3±2.3	NS
Acrophase	14.56±0.63	14.63±0.99	NS

The results show that aspects of adrenocortical function connected with regulation of electrolytes have a circadian rhythm in the very early periods of life, by contrast with glucocorticoids. Subsequent studies of adrenal function in the antenatal period and soon after birth in man may give some idea of the mechanisms lying at the basis of delayed development of the neuroendocrine and cardiovascular circadian subsystems in clinically healthy newborn infants [8, 10] with no indication of a family history of hypertension.

In older children investigated, the formation of close clusters of individual "acrophase — amplitude" pairs for SBP, DBP, and HR was observed. In agreement with this, population cosinor analysis revealed statistically significant circadian rhythms of these parameters, in agreement with results obtained previously in both adults and children. Table 3 shows that in children exposed to beta-adrenomimetics in the antenatal period there was a significantly higher mesor and numerically greater amplitude of circadian fluctuations of SBP and DBP. Positive correlation was found between the dose of the beta-adrenomimetic and the amplitude of HR ($p < 0.05$). An intergroup difference of the internal circadian time adjustment between SBP and DBP must also be noted, for in large groups of clinically healthy adults it has been shown that DBP always precedes SBP by a short time [3]. In the group of children receiving beta-adrenomimetics DBP preceded SBP in only four of nine cases, whereas in the control group, it did so in eight of the ten children. On average, the acrophase of DBP preceded the acrophase of SBP by about 15 min in the control group and by only 3 min in the group of children receiving beta-adrenomimetics ($t = 1, 704$, $p \sim 0.11$). These data, obtained by a transverse study of two groups of children during one season, require further study on a larger sample.

It was shown previously that a chronobiological approach can reveal differences in BP depending on geographical location [7], family history [10], age [4], sex [2], or treatment [8, 14]. In the present study, on a small sample of clinically healthy children, this approach revealed long-delayed consequences of antenatal exposure to beta-adrenomimetics, and this is something which calls for intensive study. The normatives of the circadian characteristics in children aged 11-13 years, obtained in the course of the investigation, will provide the basis for this study.

Thus, the spectral components of chronomes of BP and HR are manifested as early as in the premature infant, and the intensity of circennial modulation of the 3-hourly component at birth reflects the risk of diseases of the cardiovascular system later. The genetic nature of this aspect of the chronome is shown in the fact that the circennial modulation of the ultradian component is more clearly expressed in children with a family history of hypertension in the paternal line. However, exogenous factors (beta-adrenomimetics, for example), acting in the antenatal period, can also affect the structure of biological rhythms of the cardiovascular system.

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