Effect of Semax Heptapeptide on Rat Heart Activity during Acute Hypobaric Hypoxia in the Early Postnatal Period

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The effects of Semax heptapeptide on the resistance to acute hypobaric hypoxia and on hypoxic changes in the ECG chronotropic index were studied in 14- and 21-day-old pups. The resistance to hypoxia decreased with age. Hypoxic exposure caused bradycardia in both age groups. Semax reduced the bradycardiac reaction and exerted an antiarrhythmic effect without affecting the resistance to hypoxia.

Key Words: *acute hypobaric hypoxia; neonates; Semax; ECG*

Hypobaric hypoxia as an extreme condition has attracted considerable attention because of its great significance for clinical practice. Of special interest are hypoxic conditions in children during the antenatal and early postnatal periods.

Hypoxia causes a variety of symptoms, in particular, changes in the cardiovascular system, depletion of myocardial energy resources, impairment of circulation, hypotension, venous hypertension, and cerebral ischemia. The severity of cardiovascular disorders directly correlates with the duration of intrauterine hypoxia. In infants with severe asphyxia, the ECG recorded during the first postnatal days displays bradycardia with impaired intraatrial, atrioventricular, and intraventricular conductivity [3].

In this connection, it is of considerable interest to study hypoxic changes in a cardiac chronotropic index during the early postnatal period in animals.

Recently, the antihypoxic effects of the heptapeptide $ACTH_{4-7}$-Pro-Gly-Pro (Semax) have been intensely investigated [4], however its efficiency in the early postnatal period has not yet been studied.

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Therefore, the aim of the present study was to investigate hypoxic changes in the chronotropic index of ECG and the effect of Semax at different postnatal ages.

MATERIALS AND METHODS

The study was carried out on 91 pups (males and females) of outbred albino rats exposed to acute hypobaric hypoxia on the 14th and 21st days of life.

Acute hypobaric hypoxia was modeled in a pressure chamber by "lifting" to an "altitude" of 11,500 m above sea level for 1 min.

During hypoxic exposure the following indices were recorded: the time of posture loss (PLT), the time of survival (ST), i.e., the period from the end of lifting to respiratory arrest or the first agonal inspiration, and the time of restitution (RT), i.e., the period from respiratory arrest to recovery of active posture. The index of hypoxic resistance was calculated as the ST/RT ratio. Its increase indicated improved resistance to extreme oxygen deficiency [2]. If ST exceeded 10 min, the animals were classified as high-resistant and the exposure was ceased. The animals with ST below 10 min were classified as low-resistant.

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The ECG was recorded by subcutaneous electrodes implanted under Calipsol (1 mg/kg) anesthesia the day before the experiment. During hypoxia, the ECG was recorded for 5-sec periods with 5-sec intervals between them. The signal was amplified by a cardioencephaloscope and inputed to a computer to calculate the mean *RR* value for recording period (5 sec).

Semax in a dose of 0.05 mg/kg was intraperitoneally injected 5 min prior to hypoxic exposure. This dose was determined as a subthreshold for the antihypoxic effect in adult animals [1]. Control animals received an equal volume (2.5 ml/kg) of saline.

The data were analyzed statistically using the nonparametric Wilcoxon—Mann—Whitney *U* test and Fisher's exact probability test.

RESULTS

The analysis of hypoxic resistance in rats showed that in the group of 14-day-old pups the high-resistant animals were more numerous than the low-resistant (75% and 25%, respectively, Table 1), while among 21-day-old rats the number of low-resistant rats significantly increased. Hence, the resistance to hypoxia significantly decreased during postnatal ontogeny.

Semax did not affect the distribution of rats according to their hypoxic resistance (Table 1) and had no significant effects on individual indices of the low-resistant rats measured on the 14th and 21st days of life (Table 2).

The mean *RR* interval in 14-day-old low-resistant pups before hypoxia was 113.1±4.1 msec. It gradually increased from the end of "lifting" to the end of exposure and at the moment of respiratory arrest or the first agonal inspiration it attained 429.5±53.1 msec ($p<0.01$). Thus, low-resistant pups reacted to acute hypoxia by pronounced bradycardia. Semax administered to these animals did not significantly affect the dynamics of *RR* intervals: it reached 421.9±35.0 msec by the end of exposure.

In high-resistant pups of the same age, the mean *RR* interval under normal condition was 121.0±3.2 msec (no difference from low-resistant rats) and increased to 232.9±14.3 msec by the end of hypoxic episode, i.e. bradycardia was less pronounced ($p<0.01$).

TABLE 1. Effect of Semax on Resistance to Acute Hypobaric Hypoxia in Rat Pups

Age, days	Groups	High-resistant, %	Low-resistant, %
14	Control (n=20)	75	25
	Semax (n=20)	65	35
21	Control (n=27)	26	74*
	Semax (n=24)	29	71

Note. *$p<0.01$ in comparison with 14-day-old pups.

Semax did not affect the peak value but significantly reduced bradycardia within the 4-7-min exposure: the mean *RR* interval was 171.4±5.2 msec *vs.* 206.5±13.6 msec in the control group ($p<0.05$, Fig. 1, *a*).

In the control rats, hypoxia significantly increased variability of the *RR* interval: the average difference between their values in consecutive recordings increased from 2.4±0.4 msec to 24.0±4.6 msec (Fig. 2, *a*) attested to the development of arrhythmia. Semax significantly (1.9-fold) reduced variability of the *RR* interval (Fig. 2, *a*). It can be suggested that Semax exerts an antiarrhythmic effect under hypoxic conditions.

At the age of 21 days, low- and high-resistant rats did not differ in the RR interval values under normal conditions (116.5±2.8 and 115.9±3.2 msec, respectively). Semax had no effect on this index (116.2±2.7 and 122.1±3.2 msec, respectively), which is comparable with the data from 14-day-old pups.

In low-resistant rats of this age, acute hypoxia caused bradycardia: the *RR* interval increased to 452.2±16.5 msec by the end of exposure. In contrast to 14-day-old pups, the 21-day-old rats treated with Semax exhibited a significant reduction of bradycardia: the mean RR interval was shortened to 384.7± 21.3 msec ($p<0.01$). Thus, Semax did not significantly affect the individual indices of hypoxic resistance, but attenuated the negative chronotropic reaction of the heart.

Similar effects of Semax on the dynamics of RR interval were revealed in high-resistant rats of this age: within the 4-7-min exposure the mean *RR* interval was 151.1±11.1 msec *vs.* 198.9±16.2 msec in the control group (Fig. 1, *b*). The variability of the *RR*

TABLE 2. Resistance to Acute Hypobaric Hypoxia in Control and Semax-Treated Low-Resistant Rats ($M\pm m$)

Age, days	Groups	PLT, sec	ST, sec	RT, sec	ST/RT
14	Control (n=5)	45.6±11.7	235.8±81.6	128.0±32.6	2.7±1.5
	Semax (n=7)	74.2±13.5	233.6±50.1	208.0±42.5	1.1±0.1
21	Control (n=20)	36.4±3.8	236.9±33.2	261.5±35.8	1.1±0.2
	Semax (n=17)	34.3±4.4	200.5±32.3	326.6±52.3	1.3±0.5

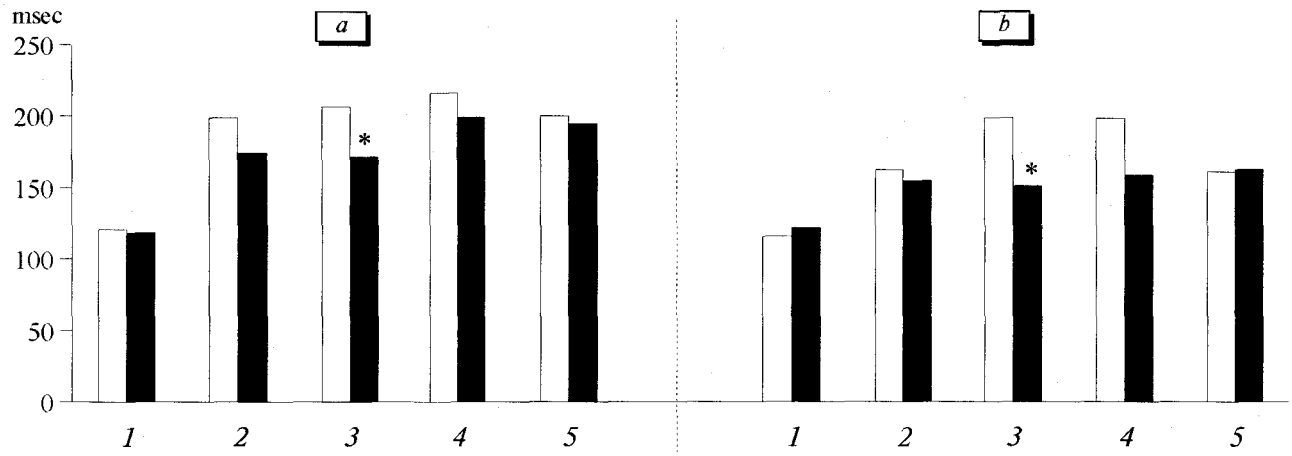

Fig. 1. *RR* intervals in high-resistant rats exposed to acute hypobaric hypoxia on the 14th (*a*) and 21st (*b*) days of life. *1)* norm, *2)* minutes 1-3; *3)* minutes 4-7; *4)* minutes 8-10 of hypoxia; *5)* after posture recovery. Here and in Fig. 2: open bars: control (saline), 14-day-old rats (n=11) 21-day-old rats (n=6); filled bars: Semax; 14-day-old rats (n=10), 21-day-old rats (n=7). *p<0.05 in comparison with the control.

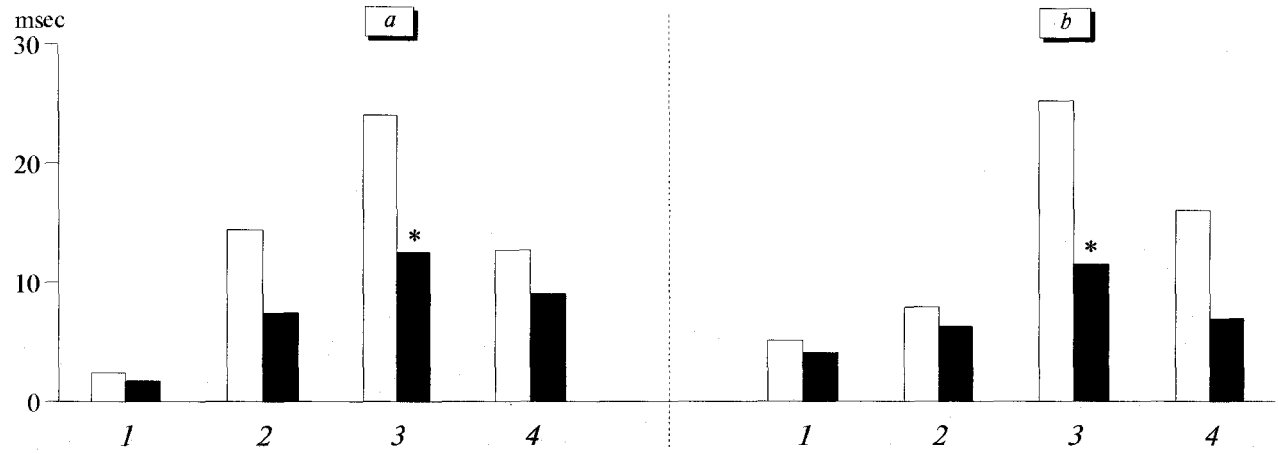

Fig. 2. *RR* interval variability in high-resistant rats exposed to acute hypobaric hypoxia on the 14th (*a*) and 21st (*b*) days of life. *1)* norm; *2)* lifting to an altitude of 11,500 m; *3)* hypoxic exposure; *4)* period from the end of hypoxic exposure to recovery of active posture.

intervals in treated animals decreased 2.2-fold (Fig. 2, *b*). These findings are comparable with the data obtained from 14-day-old high-resistant animals.

Thus, the present study demonstrated the antiarrhythmic effect of Semax under conditions of acute hypobaric hypoxia, which was manifested at different postnatal ages. No correlation between this effect and the resistance to hypoxia was found.

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