Effects of Amikacin on Maturation of the Auditory Analyzer in Rabbits

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Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 151, No. 5, pp. 536-539, May, 2011
Original article submitted March 4, 2010

We studied the dynamics of maturation of the hearing function by records of short-term latent brainstem evoked potentials and the effect of amikacin on maturation of the hearing function. The peripheral compartment of the auditory analyzer matures sooner than the central structures. Amikacin in therapeutic doses exhibited an ototoxic effect on the peripheral compartment of the auditory analyzer without impairing its central structures.

Key Words: *amikacin; rabbits; auditory analyzer; ontogenesis; short-term latent brainstem evoked potentials*

Preterm babies are born with total functional immaturity of CNS and, hence, are referred to the group at risk of hearing diseases. The situation is aggravated by the fact that by vital indications patients of this category are often subjected to intensive care and the drugs they receive can negatively affect the hearing function.

One of these drugs, amikacin, is used in clinical practice for the treatment of newborns. This potentially ototoxic aminoglycoside antibiotic was chosen for our study because it is widely used for the treatment of sepsis and bacterial infection in premature babies in Russia and in foreign countries [1,4-6,9]. The effects of amikacin on the auditory analyzer in animals during the perinatal period were experimentally studied. It is difficult to evaluate hearing function at this stage, because the organ is in the state of maturation during this period. In order to differentiate between age-specific characteristics and changes associated with ototoxic injury, it is essential to know age-specific norm of the developing animal.

We traced the dynamics of auditory function maturation by recording short-term latent brainstem (auditory) evoked potentials (SSEP) and evaluated the effect of amikacin on the hearing function during maturation of the auditory analyzer.

MATERIALS AND METHODS

The study was carried out on rabbits (according to previous data indicating the possibility of using these animals for studies of the effects of various factors on maturation of the hearing function during the perinatal period [7]).

Control group consisted of 12 intact male and female rabbits (animal age 12-45 days); hearing function was evaluated by SSEP recording. Evoked potentials could be clearly recorded on day 12 of life. The potentials were recorded in each animal weekly until stabilization of the amplitude and time characteristics. Hence, the studies were carried out in all animals on days 12, 19, 26, 35, and 45 of life.

Experimental group consisted of 13 animals receiving amikacin in a therapeutic dose (7.5 mg/kg twice daily for 7 days) starting from day 12 of life. Seven days after antibiotic therapy, 3 evaluations of the auditory function was evaluated 3 times on the same days as in the control group (days 26, 35, 45).

Evoked potentials in response to 1-100 dB were recorded in the centromastoidal lead via subcutane-

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ous needle electrodes as described previously [2]. The latency was measured from the moment of acoustic stimulus in earphone to the positive peak of the first wave. The click intensity corresponded to the peak pulse values on the display (device manufactured by Biomedica Firm). SSEP were recorded after intramuscular injection of 2% rometar (0.1 ml/kg), a myorelaxant and analgesic (drugs of this kind were inessential for recording of the amplitude and time characteristics of cerebral potentials [5]).

RESULTS

The threshold values of the detected evoked potentials recorded before day 12 of life varied from 60 to 80 dB, which attested to a significant variety in the degree of the auditory analyzer maturation in different animals. SSEP were clearly recorded only starting from day 12 of life. These results completely coincided with the data of other authors [8]. During the subsequent 5 weeks, studies of the hearing function revealed gradual maturation of the auditory analyzer, which manifested in reduction of the perception threshold and shortening of the latency from the moment of stimulation to the appearance of the first peak on the recorded SSEP curve.

Sound perception thresholds decreased significantly ($p<0.05$) every week until day 26 of life (Table 1). Later the threshold values only slightly decreased.

Changes in the latency of the first SSEP peak after stimulation of different intensity during various periods of the study are presented in Fig. 1. The data were approximated by the second order polynomial $L=a+b\times I+c\times I^2$, where a, b, and c coefficients were found by the method of least squares. These curves presented changes in the relationship between the peripheral time of stimulation conduction and stimulus intensity, that is, the time from the moment of acoustic stimulus delivery to the appearance of the pulse discharge in spiral ganglion neurons. The approximation curves reflecting the relationship between the latency of the first peak and stimulus intensity differed significantly ($p<0.02$) on days 12, 19, and 26 by. On the other hand, no appreciable differences between the approximation curves on days 26, 35, and 45 were found, which agreed with the results of evaluation of sound perception thresholds. Obviously, maturation of the peripheral compartment of the auditory analyzer in animals was the most intense during the first weeks of life. By day 26, the peripheral compartment of the auditory analyzer in rabbits functionally (according to SSEP) did not change much. The same was shown by estimated data on the shift time, difference in the latency of the first SSEP peak at intensities of 100 and 30 dB (Table 2). This parameter differed significantly ($p<0.05$) in animals only on day 12 of life in comparison with the parameter during later periods of development.

In parallel with this, we studied the dynamics of the central conduction time, that is, the time of nerve pulse propagation in brainstem structures (Table 3).

Similarly as in other animals, the central conduction time did not depend on stimulus intensity [2]. In rabbits, central conduction time at the age of 12, 19, and 26 days was significantly longer ($p<0.05$) than at the age of 35 days. This indicated slower conduction in brainstem structures and presumably reflected im-

TABLE 1. Peak 1 Thresholds during Different Periods in Intact Animals and after Amikacin Treatment ($M\pm m$; dB)

Day of observation	Group	
	control	experiment
12	42.0±4.1	-
19	30.0±2.7	-
26	18.0±2.6	28.8±2.6
35	17.1±2.2	24.0±2.3
45	14.6±1.8	20.8±2.3

Note. All data are significant ($p<0.05$).

TABLE 2. SSEP Peak 1 Latency Shift Time at Intensities of 100 to 30 dB ($M\pm m$; ΔL, msec)

Day of observation	Group	
	control	experiment
12	1.4±0.1	-
26	1.10±0.04	0.90±0.08
35	1.10±0.05	0.95±0.05
45	1.11±0.05	0.86±0.07

TABLE 3. Stimulus Conduction Time from Peak 2 to Peak 4 at Stimulus Intensity of 60 dB ($M\pm m$; $L_{2\text{-}4}$, msec)

Day of observation	Group	
	control	experiment
12	2.40±0.36	-
19	2.13±0.14	-
26	1.86±0.17	1.82±0.14
35	1.75±0.19	1.77±0.10
45	1.74±0.22	1.77±0.08

maturity of the central structures during that period. The absence of appreciable differences in the central time of conduction between the experimental and control groups suggests that amikacin does not modify the state of the stem structures. Comparative analysis of the time parameters of peripheral and central conduction indicated delayed maturation of the central compared to peripheral structures.

Amikacin treatment modified the hearing function primarily through changes in the peripheral compartment of the auditory analyzer. The peak detection thresholds increased significantly after antibiotic treatment, which was most pronounced one week after the treatment. Later, the thresholds remained significantly elevated (Table 1). The relationship between the SSEP peak 1 latent period (L_1) and the stimulus intensity (I) after amikacin treatment also changed significantly (Fig. 2). The latent periods were prolonged, particularly at low intensities. This was paralleled by reduction of the time difference (peak shift) between the latent periods of SSEP peak 1 at intensities of 30 and 100 dB (Table 2). This fact, *i.e.* shorter time difference in the latent peak values, has been described in clinical reports as an objective electrophysiological validation of the presence of a well-known phenomenon, accelerated increase of loudness [3].

Studies of the central time of conduction after amikacin treatment showed no appreciable differences between the control and experimental groups (Table 3). These results suggested that amikacin in the dose used in our experiments was inessential for central structures of the acoustic route.

Hence, we conclude that evoked potentials (according to SSEP recording) are clearly recorded in rabbits from day 12 of life. The maturation of the peripheral compartment of the auditory analyzer in rabbits was completed by day 26 of life, which manifested in stabilization of the threshold values and by the absence of significant differences in approximation curves reflecting the relationship between the first peak latency and stimulus intensity during that period and subsequent observations. According to recorded SSEP, maturation of the central compartments of the auditory analyzer is over after 35 days of life, which was shown in SSEP curve by the absence of statistically significant differences in the central conduction time only between days 35 and 45 of life. The therapeutic doses of amikacin exhibited an ototoxic effect on the peripheral compartment of the auditory analyzer without functionally impairment of the stem structures.

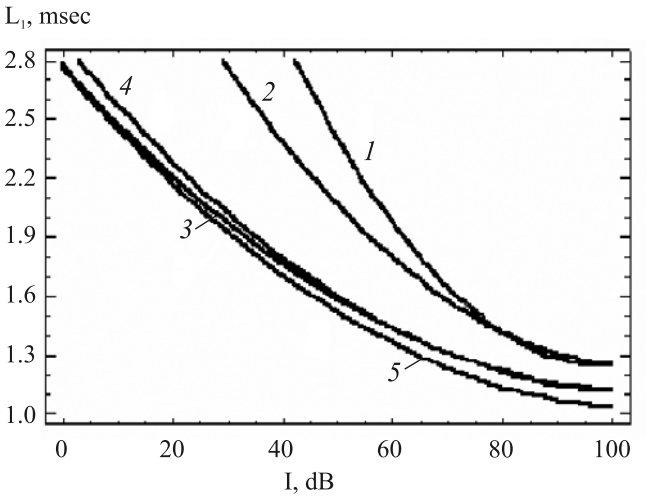

Fig. 1. Relationship between latency of the first SSEP peak L_1 and stimulus intensity I. *1*) 12 days; *2*) 19 days; *3*) 26 days; *4*) 35 days; *5*) 45 days.

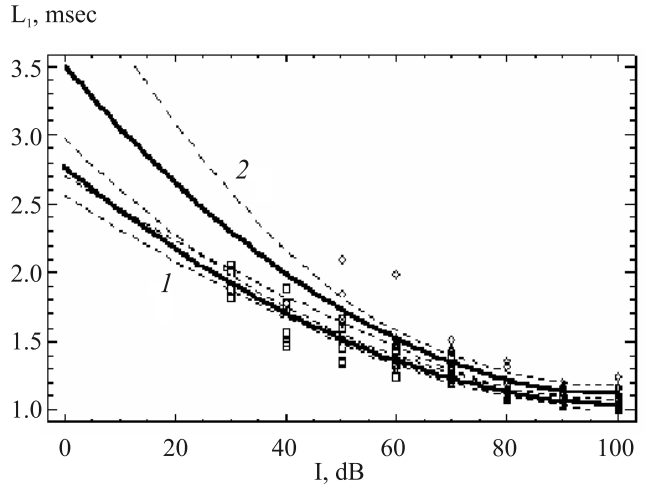

Fig. 2. Relationship between SSEP peak 1 latency L_1 and stimulus intensity I on day 45 of life in normal (*1*) and after amikacin course (*2*). Continuous lines: polynomial approximation; interrupted lines: limit the 95% confidence areas. Experimental points: squares: normal status; rhombi: amikacin.

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