Peculiarities of Nerve Conduction Block Produced by Lidocaine and Ajmaline

N. A. Mangusheva and L. L. Katalymov

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 143, No. 3, pp. 262-266, March, 2007
Original article submitted September 5, 2006

The development of tonic and use-dependent block of nerve conduction under the effect of antiarrhythmic drug ajmaline and local anesthetic lidocaine was examined on sciatic nerve of *Rana ridibunda*. Ajmaline and lidocaine attenuated the amplitude of action potential by half during 120 and 13 minutes, respectively. Ajmaline produced virtually immediate use-dependent block of conductance, while it was minor in lidocaine-treated nerve preparation.

Key Words: *lidocaine; ajmaline; nerve; conduction block*

In addition to tonic block (TB) of nerve conduction inducing persistent attenuation of action potential (AP) under the action of Na^+-channel blockers, there exists a use-dependent or cumulative block (UDB) which inhibits AP and finally eliminates it during the rhythmic nerve stimulation [5,8,9]. UDB makes it possible to apply local anesthetics at very low concentrations in order to diminish their toxicity and to enhance the effect, when needed, by rhythmic stimulation. The phenomenon of UDB found a way to clinical pharmacology. Specifically, some drugs potentiating UDB of sodium channels efficiently moderate the neurophathic pains caused by cancer [3,4,11].

Similar to local anesthetics, the antiarrhythmic preparations also block sodium channels, which explains actuality to examine their potency as local anesthetic drugs. However, some peculiarities of their TB and UDB were little studied.

Our aim was to comparatively study TB and UDB of nerve conduction under the effect of local anesthetic lidocaine and cardiac antiarrhythmic ajmaline.

MATERIALS AND METHODS

The experiments were carried out at 20-22°C on sciatic nerves (n=48) isolated from *Rana ridibunda*. After isolation, the nerve was placed for 30-40 min into Ringer solution containing (in mM): 114.0 NaCl, 2.5 KCl, 2.0 $CaCl_2$, 10.0 HEPES (pH 7.4). Then it was mounted in a humid chamber onto two pairs of electrodes: stimulating (proximal) and recording (distal).

The recorded data were the initial amplitude of AP evoked by a single supramaximal stimulus and a series of AP elicited by rhythmic stimulation applied at the rate of 10, 50, and 100 Hz during 400 msec. Then the nerve was washed with Ringer solution containing 10 mM ajmaline (Sigma) or 10 mM lidocaine (Sigma), thereafter it was transferred into experimental chamber to record changes in AP amplitude. When AP evoked by a single stimulus decreased to 75 and 50% of the initial value, the nerve was rhythmically stimulated to assess UDB. The signals were amplified and recorded in an UBNK-V electrophysiological complex (Experimental Workshop of Research Institute of Experimental Biology and Medicine, Siberian Division of the Russian Academy of Sciences, Novosibirsk).

The data were processed statistically using Student's t test.

RESULTS

In control Ringer solution, rhythmic stimulation applied at the rate of 10, 50, and 100 Hz decrea-

Ul'yanovsk State Pedagogic Institute, Russia. ***Address for correspondence:*** kll37@mail.ru. L. L. Katalymov

0007-4888/07/1433-0295

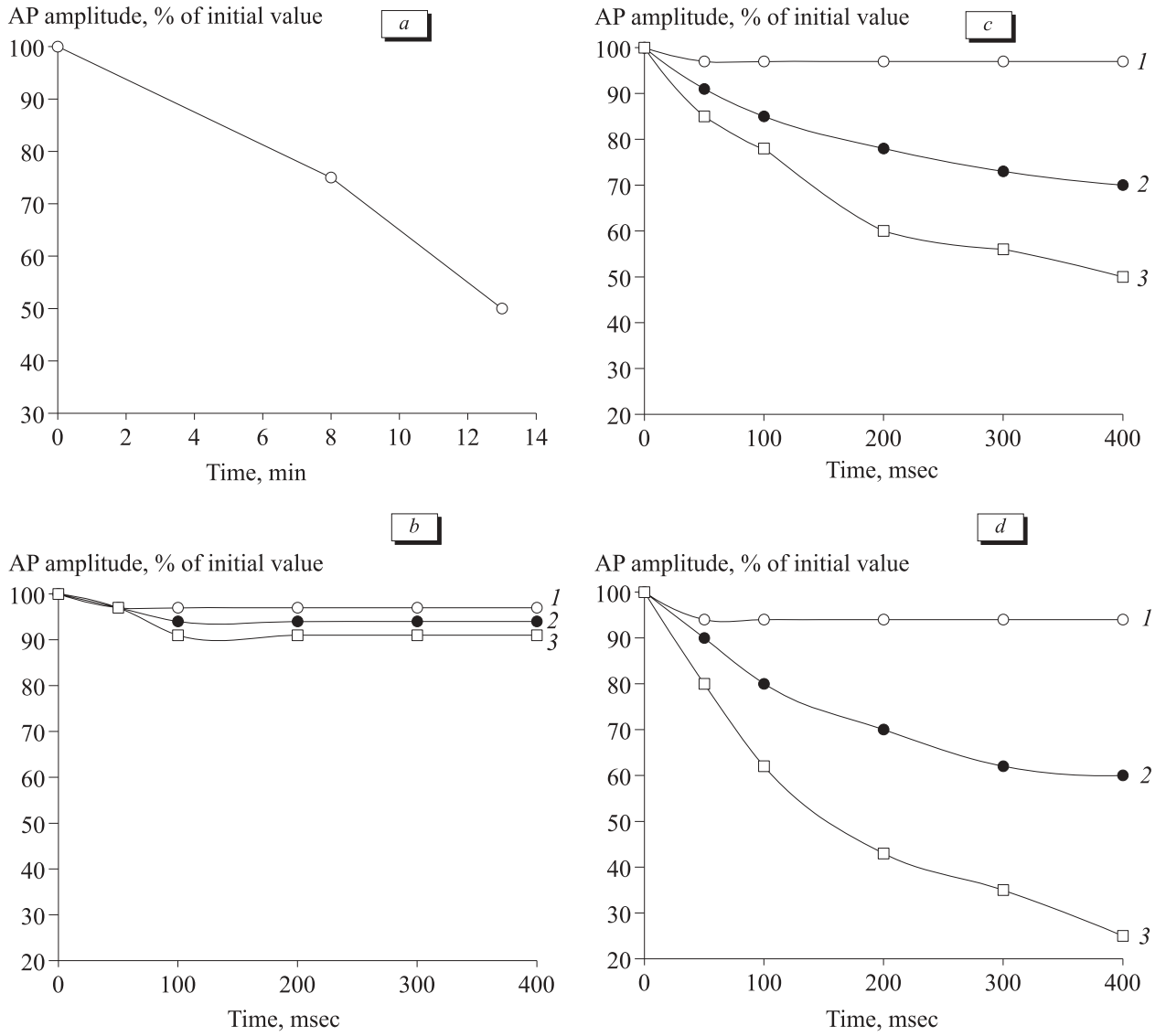

Fig. 1. TB and UDB of conductance in whole nerve produced by lidocaine. *a*) decrease in AP amplitude in response to a single stimulus. UDB of conduction during AP decrease under the action of lidocaine to 75 (*b*) and 50% (*c*) from the initial value; *d*) changes in AP amplitude after bathing in Ringer solution; stimulation rate was 10 (*1*), 50 (*2*), and 100 Hz (*3*).

sed AP by 3, 6, and 9% from the initial value (Fig. 1, *b*).

Lidocaine produced TB (assessed by a single supramaximal stimulus) and decreased AP amplitude to 75% from the initial value over 8.0±0.9 min. During this period, rhythmic stimulation applied at rates of 10, 50, and 100 Hz for 400 msec decreased AP by 3, 30, and 50% (Fig. 1). After the end of stimulation, AP virtually immediately returned to the level observed during the response to a single stimulus.

The AP amplitude in response to a single maximum stimulus under the effect of lidocaine decreased to 50% of the initial value over 13.0±1.2 min. During this period, rhythmic stimulation applied at rates of 10, 50, and 100 Hz for 40 msec decreased AP by 6, 40, and 75% (Fig. 1, *c*). Washout in control Ringer solution restored the amplitude of AP after 32.2±0.4 min (Fig. 2, *a*).

In Ringer solution containing 10 mM ajmaline, the amplitude of AP decreased to 75% of the initial value over 60±2 min. Rhythmic stimulation at rates of 10, 50, and 100 Hz under these conditions completely eliminated AP after 320, 75, and 40 msec, respectively (Fig. 3, *b*); 0.5-1.0-sec pause in rhythmic stimulation restored the AP amplitude to that produced by a single stimulus.

Ajmaline decreased the amplitude of single AP by half over 120.0±2.6 min (Fig. 3, *c*), *i.e.* 9.2-fold more slowly than lidocaine. Rhythmic stimulation rapidly eliminated AP. This block was induced after stimulation at the rates 10, 50, and 100 Hz over 190, 25, and 12 msec, respectively (Fig. 3, *b*); 0.5-

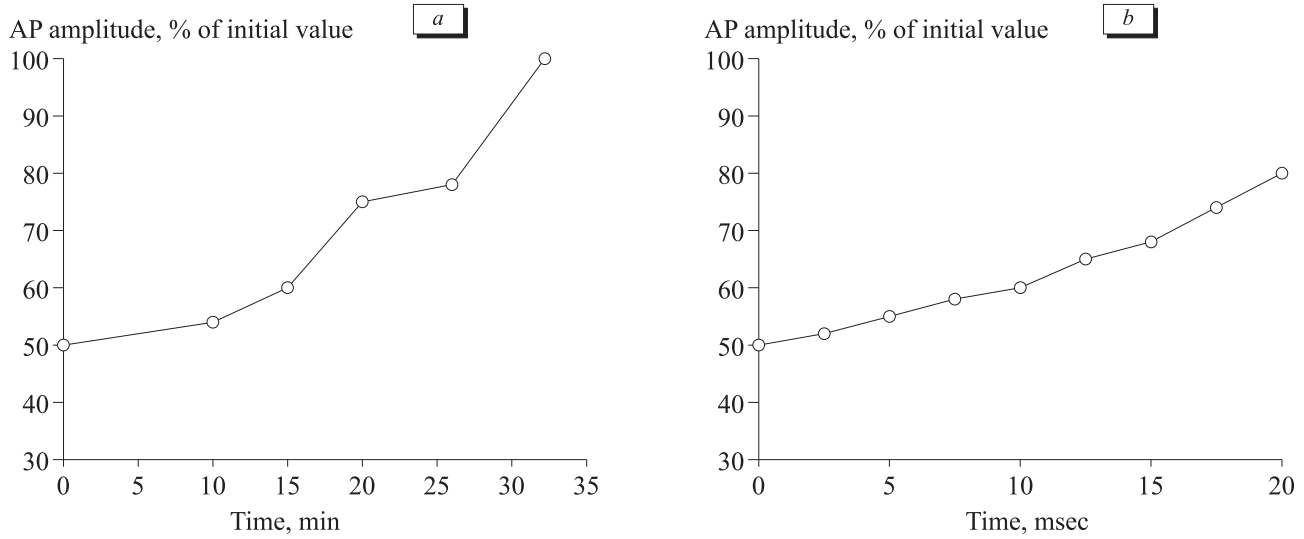

Fig. 2. Restoration of AP amplitude during washout in Ringer solution after application of lidocaine (*a*) and ajmaline (*b*).

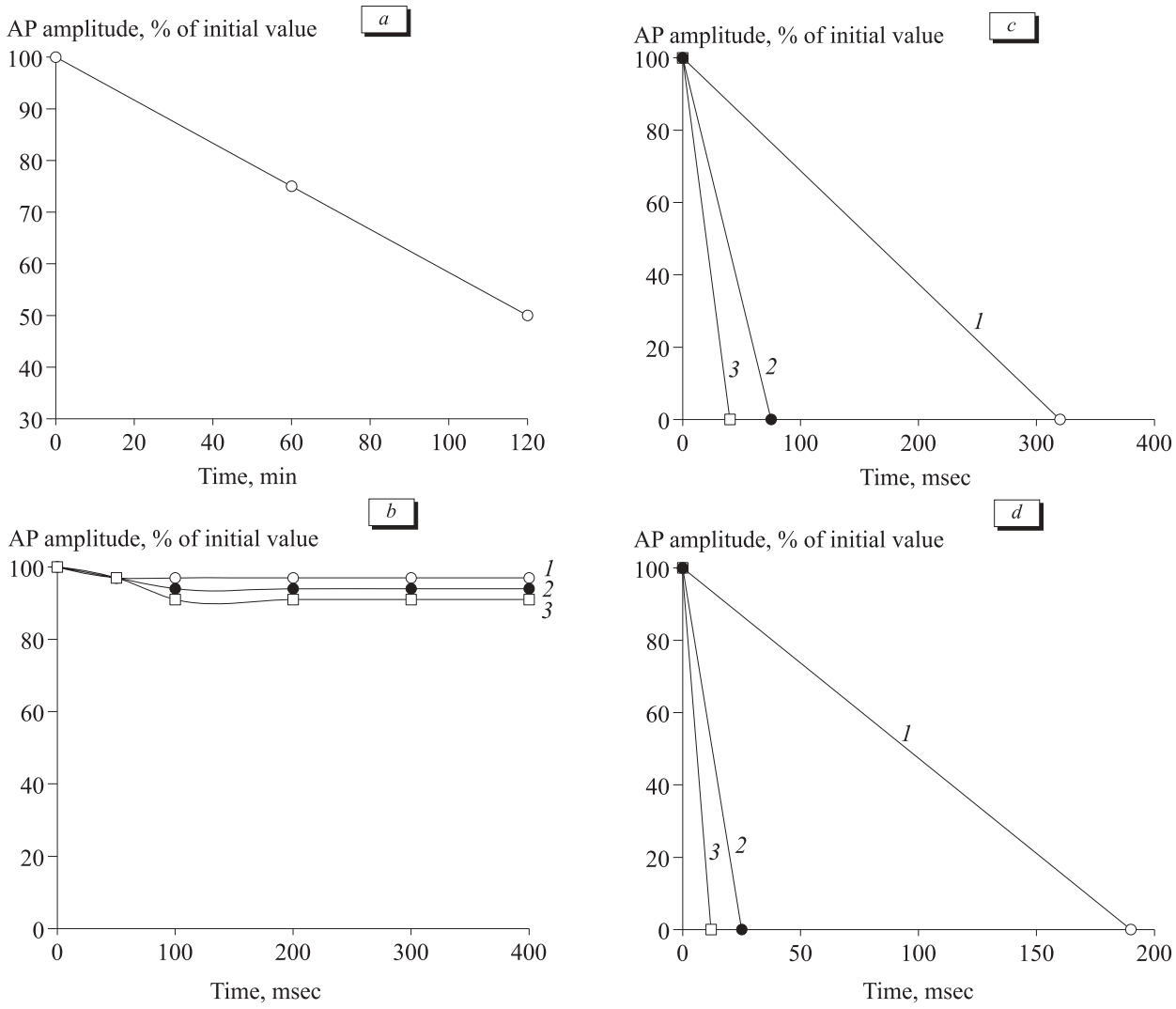

Fig. 3. TB and UDB of conductance in whole nerve under the effect of ajmaline. *a*) decrease of AP amplitude was tested by single stimuli. UDB of conductance in AP amplitude decrease to 75 (*b*) and 50% (*c*) from the initial value; *d*) changes in AP amplitude during washout in bathing Ringer solution. Stimulation rate was 10 (*1*), 50 (*2*), and 100 Hz (*3*).

sec pause in stimulation restored AP amplitude to the value of the response to a single stimulus. After washout in a large volume of Ringer solution, AP amplitude recovered very slowly (over 20±1 h, *i.e.* by 37.5 times slower than during washout from lidocaine). The comparatively slow development of TB under the action of ajmaline is probably related to its large molecular weight, hydrophobic nature, and peculiarities of spatial structure of its molecule composed of several condensed aromatic heterocycles.

Despite significant difference in the parameters of conduction block produced by lidocaine and ajmaline, the mechanisms of their action seem to be similar. Both drugs belong to tertiary amines existing in aqueous solution in two forms: neutral and positively charged (protonated). Both drugs can interact with open and inactivated sodium channels [5-8]. According to modulated receptor theory [1,2,5], neutral molecules of the anesthetic can enter the cytoplasm across membrane lipid matrix. Under the action of low pH in the cytoplasm, some anesthetic molecules become protonated and enter the Na^+ channel in this charged form [5,8,10].

During electrical stimulation, the number of open sodium channels considerably increases, so charged molecules of the anesthetic enter and block them in accumulative manner. Pronounced ajmaline-induced UDB is probably explained by the fact that the complex ajmaline-inactivation gate is more stable than the similar complex with lidocaine.

TB of sodium channels is little studied. Probably, lidocaine and ajmaline interact with inactivation gate particles of rapidly inactivating sodium channels in the neutral form and delay their transition into the re-active state [1,12]. This process is known as "slow sodium inactivation" [8]. However, the block of some sodium channels due to its spontaneous opening cannot be excluded.

This study was supported by the Russian Foundation for Basic Research (grant No. 05-04-48883).

REFERENCES

1. N. A. Mangusheva, L. V. Baidakova, and S. V. Revenko, *Byull. Eksp. Biol. Med.*, **113**, No. 3, 248-250 (1992).
2. S. V. Revenko, L. V. Borovikova, and V. V. Ermishkin, *Ros. Fiziol. Zh.,* **85**, No. 1, 119-127 (1999).
3. F. Bernard, S. T. Kudnig, and E. Monnet, *Vet. Surg*., **35**, No. 3, 252-258 (2006).
4. W. G. Brose and M. J. Cousins, *Pain*, **45**, No. 2, 145-148 (1991).
5. J. F. Butterworth, 4th and G. R. Strichartz, *Anesthesiology*, **72**, No. 4, 711-773 (1990).
6. A. P. Gokin, B. Philip, and G. R. Strichartz, *Ibid.*, **95**, No. 6, 1441-1454 (2001).
7. M. Guven, T. Mert, and I. Gunay, *Int. J. Neurosci.*, **115**, No. 3, 339-349 (2005).
8. B. I. Khodorov, *Ann. N.Y. Acad. Sci.*, **625,** 224-248 (1991).
9. D. S. Ragsdale, T. Scheuer, and W. A. Catteral, *Mol. Pharmacol.*, **40**, No. 5, 756-765 (1991).
10. M. L. Roy, and T. Narahashi, *J. Neurosci*., **12**, No. 6, 2104-2111 (1992).
11. D. L. Tanelian, W. G. Brose, *Anesthesiology*, **74**, No. 5, 949-951 (1991).
12. Y. Zilberter, L. Motin, S. Sokolova, *et al*., *J. Mol. Cell. Cardiol*., **23**, Suppl. 1, 61-72 (1991).