PHARMACOLOGY AND TOXICOLOGY

Antiedematous and Edematous Effects of Local Anesthetic RU-353 Applied to Various Regions of the Medulla Oblongata

A. P. Galenko-Yaroshevskii, L. Z. Tel'*, and S. P. Lysenkov

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 138, No. 12, pp. 635-637, December, 2004
Original article submitted June 23, 2004

Experiments on random-bred albino rats showed that application of local anesthetic RU-353 to the dorsal nuclei of the vagus nerve produced edematous or antiedematous effects in the lungs. Our findings open new vistas in prevention of centrogenous forms of water imbalance in the lungs.

Key Words: *lungs; edema; local anesthetic RU-353; dorsal nuclei of the vagus nerve*

Published data suggest that violent interventions into the grey wing region induce pulmonary edema [4,5]. The role of some hypothalamic and medullar structures (specifically, dorsal nuclei of the vagus) in the development of centrogenous forms of pulmonary edema was experimentally proven [2]. Local electrolytic destruction of this area revealed functional heterogeneity of the dorsal vagal nucleus, which manifested in their different effects on pulmonary hydration [3]. However, functional interrelations between the rostral and caudomedial regions of the dorsal nucleus still remain unclear. Here we evaluated the possibility of pharmacological regulation of hydration processes in the lungs and pharmacological prevention of pulmonary edema of the central genesis.

MATERIALS AND METHODS

Acute experiments were performed on 75 random-bred albino rats (170-220 g) anesthetized with ether. The animals were placed in a Zcentagothai stereotaxic apparatus so that the ear-teeth plane of the head was inclined by 40° relative to the horizontal plane. Stereotaxic coordinates were determined according to the laboratory-made atlases and coordinate frames (Fig. 1). The most caudal pole of the rhomboid fossa (*obex*) was taken as the reference point; while the frontal plane lying 10 mm rostral to *obex* was assumed as zero plane (0.0). The planes (P) rostral to *obex* by 1, 2, 3, and 4 mm were named as planes 9.0, 8.0, 7.0, and 6.0, while those located 1, 2, 3, and 4 mm caudal to *obex* were termed as planes 11.0, 12.0, 13.0, and 14.0, respectively. Anesthetic RU-353 (laboratory code, 0.0005%) was injected with a microsyringe in a volume of 5 μ into structures of the medulla oblongata. This agent effectively blocks Na^+, K^+, and Ca^{2+} channels [1]. For modulation of the rostral regions of the dorsal vagal nuclei application of the blocker was used. To this end, the atlantooccipital membrane was cut and the input to the sylvian aqueduct was atraumatically blocked with a cotton plug. A sponge soaked with anesthetic solution was applied to the rostral regions of the nuclei. Water content in the lungs was determined postmortem by calculating the percentage of dry-to-wet mass ratio of the organ (index of dry residual). The heads were fixed in 10% neutral formaldehyde. Serial sections (40 μ) were cut using a freezing microtome.

Krasnodar Regional Medical Research Center; *Akmola State Medical Academy, Astana. ***Address for correspondence:*** lsp@mail.ru. S. P. Lysenkov

0007-4888/04/1386-0562

The rats were subdivided into four experimental groups. The first group rats were not given anesthetic RU-353 after surgery (control; *n*=35). In the second group (*n*=15), the anesthetic agent was injected into medulla oblongata structures. In the third group (*n*=15), the anesthetic was applied to the rostral region of the dorsal vagal nuclei. In the fourth group (*n*=10), the blocker was simultaneously injected into the caudomedial medulla and applied to the rostral part of the dorsal nucleus.

The results were statistically analyzed by Student's t test.

RESULTS

In group 2, injections of RU-353 within planes 10.2-10.0 (Fig. 1) increased water content in the lungs (solid residual 13.35±0.78% *vs.* 21.20±0.17% in control; $p<0.001$). The typical clinical picture consisted in markedly disturbed rhythm and depth of respiration followed by the appearance of acrocyanosis and far audible rale, and, eventually, death of the animals after 85.5±15.1 min. Postmorten examination revealed multiple small and large punctate dark-red hemorrhages in the lungs. On sections foamy fluid was detected. In most animals, pink foamy fluid was observed at the level of bifurcation. RU-353 injections into the adjacent medullar regions had no effect on water balance in the lungs (4 rats).

In group 3, application of anesthetic RU-353 onto the rostral part of the dorsal vagal nuclei (Fig. 1) did not cause fatal respiratory changes and animal death, but bradi- and hyperpnoea were noted. The rats were killed 30 to 90 min postinjection. The gravimetric analysis showed that water content in the lungs of these rats even decreased compared to the control (22.54±0.13%, $p<0.01$). Macroscopic picture of the lungs in group 3 only slightly differed from that in the control group.

Simultaneous injections of RU-353 into the caudomedial regions and application to the rostral regions of vagal dorsal nuclei (Fig. 1) produced no shifts in pulmonary water balance. Clinical picture in this group was characterized by progressive respiratory depression followed by apnea. Although the rats died during 28-46 min, autopsy showed their lungs were similar to those in control rats (solid residual 21.60±0.23%, $p<0.5$).

These findings confirm functional heterogeneity of the dorsal vagal nuclei: pulmonary edema developed only after blockade of neuronal activity in the caudomedial regions of the dorsal vagal nuclei. It is most likely that this edematous effect is mediated by the rostral structures of the nucleus, which normally suppress the edemogenic influences coming to the lungs from the caudomedial structures of the nucleus. This conclusion is based on the fact that blockade of the latter structures is accompanied by a decrease in pulmonary water content. These data confirm the idea that the rostral part of the nucleus represents a relay-collector unit that provides optimal water balance in the lungs. In fact, simultaneous inhibition of neuronal activity with RU-353 in both rostral and caudomedial parts of vagal dorsal nuclei did not change the pulmonary water content.

Under physiological conditions the optimal balance between neural activities in two functionally dif-

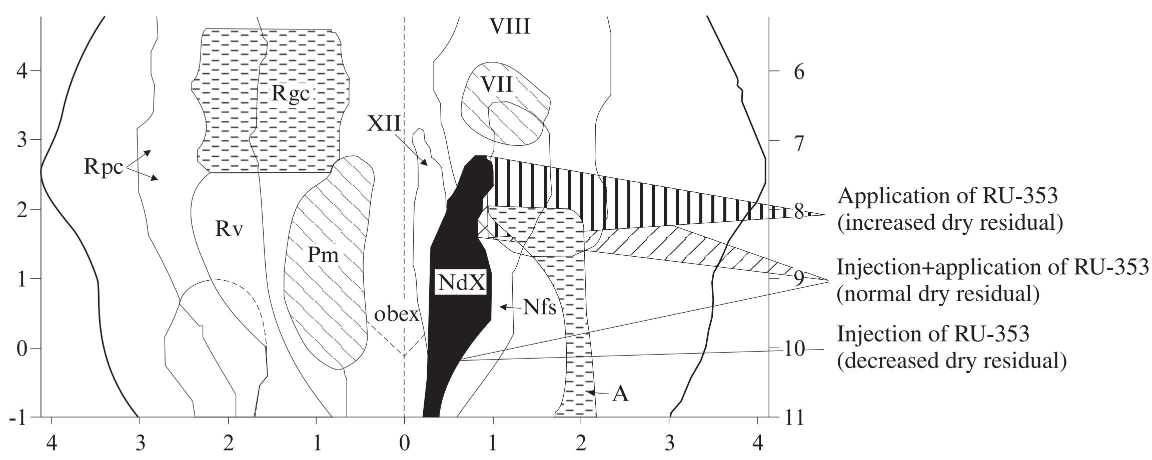

Fig. 1. Edematous and antiedematous effects of local anesthetic RU-353 applied to various regions of the dorsal nucleus of the vagus (NdX). A horizontal section of the medulla oblongata with some major structures ventral to NdX. Ordinates: Left vertical scale shows the distance (in mm) from the caudal angle of the rhomboid fossa (from *obex*). Right vertical scale shows the numbers of frontal planes (P) starting from the zero plane (10 mm rostral to *obex*). Abscissa: distance from midline (in mm). XII: nuclei of hypoglossal nerves; Nfs: solitary tract nuclei; Pm: paramedian reticular nuclei; RGc, Rv, and Rpc: reticular nuclei; A: nucleus ambiguous, VII: facial nuclei; VIII: vestibular nuclei.

ferent subdivisions of the vagal nucleus determining predomination of hydration processes in the lung tissue and on the alveolar surface prevents drying and damage of the alveolae exposed to air.

Other data suggest that the function of the relay neurons located in the rostral part of the nucleus can be impaired in case of inappropriate input signals received by these neurons, in particular, after injection of Na^+ channel activator aconitine [4]. Similar situations also can occur in medical practice, for example, under conditions of cerebral hypoxia, craniocerebral trauma, cerebral hemorrhage, intoxication with neurotropic poisons, *etc*.

Thus, we revealed some peculiarities in the organization of the neural mechanisms controlling water balance in the lungs and experimentally demonstrated the possibility of their modulation. Our findings open new prospects in the development of novel methods for correction of hydration processes in the lungs, which can be used in clinical practice.

REFERENCES

1. S. P. Lysenkov, L. Z. Tel', A. P. Galenko-Yaroshevskii, and V. A. Anisimova, *Byull. Eksp. Biol. Med.*, Suppl. 3, 9-13 (2002).
2. L. Z. Tel' and S. P. Lysenkov, V*opr. Neirokhir.*, No. 4, 21-25 (1987).
3. L. Z. Tel' and S. P. Lysenkov, *Central Neural Mechanisms of Pulmonary Edema* [in Russian], Alma-Ata (1989).
4. N. Doba and D. Reis, *Circ. Res.*, **32**, 584-593 (1973).
5. D. Reis, N. A. Nathan, and N. Doba, *Clin. Exp. Pharmacol. Physiol.*, No. 2, 179-183 (1975).