MORPHOLOGICAL AND FUNCTIONAL CHANGES IN THE ADRENERGIC INNERVATION OF THE CEREBRAL ARTERIES AFTER BILATERAL ELECTRICAL STIMULATION OF THE LOCUS COERULEUS

K. G. Tayushev, A. P. Pugovkin,
E. A. Dergacheva, and V. M. Klimenko

UDC 616.133.33-018.86-02:
615.844.032.81

KEY WORDS: cerebral arteries; locus coeruleus; cerebral circulation.

A large part of the intramural nervous apparatus of the cerebral arteries has been shown [3, 10] to consist of adrenergic fibers and endings, which have their source in certain brain-stem nuclei. Nevertheless, this feature, so important from the morphological standpoint, correlates only weakly with data on the role of the neurogenic component in the regulation of the cerebral circulation [2, 4, 6, 7]. This disagreement is largely attributable to the inadequate number of morphological and functional investigations which have been undertaken to test the effect of various influences on the intracranial sources of innervation of the cerebral vessels. Yet investigations of this kind are important to study the state of the nervous apparatus of the blood vessels under clinical conditions, for example, in severe lesions of the CNS accompanied by disturbances of the cerebral circulation [7].

Among the brain-stem nuclei that participate in the adrenergic innervation of the cerebral arteries [3, 4] the nuclei of the locus coeruleus (NLC) are particularly interesting. We know that they consist mainly of adrenergic neurons, innervating the intracerebral arteries [14, 15], which exert an influence on the cerebral blood flow. However, the functional role of these neurons, as well as the representation of their processes and endings in the region of the arteries of the circle of Willis have been inadequately studied [1, 8, 11, 13]. The causes of the inconsistency of the changes in the local blood flow, certain biochemical parameters of the circulation, and also catecholamine levels in different parts of the brain in response to stimulation of NLC still remain unexplained [1, 8, 9, 12].

In this paper we analyze the morphological and functional states of adrenergic structures of the intramural nervous apparatus of the basilar and cerebral arteries during electrical stimulation of NLC in chronic experiments.

EXPERIMENTAL METHOD

Adrenergic nervous structures were studied in the proximal fragments of the basilar and the anterior, middle, and posterior cerebral arteries, and also the pial vessels on the basal surface of the medulla of 19 adult chinchilla rabbits. Bilateral electrical stimulation of NLC with square pulses of current (0.05 mA, 1 msec, 50 Hz) was applied through stereotaxially implanted unipolar nichrome electrodes with a diameter of cross section of 200 μ. The location of the electrode tip corresponded to coordinates: P = 19.0 mm, H = 9.0 mm, L = 1.1 mm. According to the results of histological verification, the uninsulated electrode tips were located as a rule in the rostral part of the nuclei to be tested (stereotaxic operations were performed in the Department of General Pathology and Pathophysiology, Institute of Experimental Medicine, Academy of Medical Sciences of the USSR. The authors are grateful to Candidate of Biological Sciences I. P. Tsvetkova for his help with the histological verification of the position of the electrodes). The experimental group consisted of seven rabbits, control group 1 (intact animals) of six rabbits, control group 2 (with electrodes in NLC, without stimulation) of five rabbits, and eight and two rabbits respectively underwent mock operations. Daily stimulation of NLC for 1 h began 1 week after the stereotaxic operation. Five of the seven rabbits received 3-5 sessions of stimulation, and the other two re-

A. L. Polenov Neurosurgical Research Institute, A. I. Gertsen Pedagogic Institute, and Research Institute of Experimental Medicine, Academy of Medical Sciences of the USSR, Leningrad. (Presented by Academician of the Academy of Medical Sciences of the USSR B. I. Tkachenko.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 103, No. 2, pp. 218-221, February, 1987. Original article submitted January 28, 1986.

 0007-4888/87/0002-0250$12.50

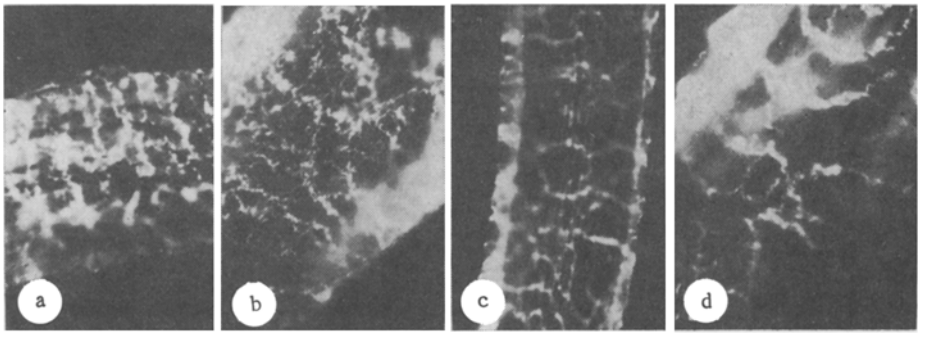

Fig. 1. Adrenergic nerve structures of anterior (a, c) and middle (b, d) cerebral arteries in experimental rabbits (five sessions of stimulation) (a, b) and intact rabbits (c, d). Magnification 60×.

ceived 10 sessions each. Each experimental animsl was brought out of the experiment along with the controls. Adrenergic nerve structures were demonstrated by means of a 2% solution of glyoxylic acid in isotonic incubation medium (20% sucrose) and studied under the LYUMAM I-2 microscope. The density of distribution of the fibers in the composition of the vascular nerve plexuses was estimated with the aid of an ocular grid [5] and the concentrations of catecholamines by the intensity of luminescence of the varicose expansions, measured by an FMÉL-1 cytophotometer. The density of distribution of the fibers was determined on the basis of measurements in 20 small squares of the ocular grid (at 64 points in each square) and the intensity of luminescence was estimated on the basis of 50 measurements in the region of each vessel. The results were expressed as percentages of the control. The data were subjected to statistical analysis by Student's paired t test. Differences were considered to be significant at the $P < 0.05$ level.

EXPERIMENTAL RESULTS

The cerebral vessels of the experimental and control animals contained intramural adrenergic nerve plexuses, whose architectonics agreed completely with data in the literature [3, 4, 10]. Preliminary visual assessment of the material showed that besides clearly distinguishable, brightly luminescent fibers, thin fibers, mainly oriented transversely, with an extremely indistinct luminescence, were constantly present in the composition of the plexuses. The latter could be definitely diagnosed only under high power (90) of the microscope. These fibers with weak activity were mainly observed in the experimental animals, less frequently in the animals of control group 2. The opposite relationship held good for the more active, brightly luminescent fibers. On the whole, under average power of the microscope (40), which was used for the quantitative investigation, adrenergic plexuses in the experimental animals appeared to be denser (Fig. 1).

On the basis of this observation, even before the quantitative estimations, it could be concluded that the procedure of insertion of the electrodes, as well as the mock operation (no differences were observed after these procedures), led to a decrease in density of the catecholamine-saturated adrenergic nerve structures. This conclusion was subsequently confirmed quantitatively. The density of arrangement of the fibers in control 2 was 6.4 ± 2.5% less than in control 1, and there was a simultaneous decrease in the intensity of luminescence of the remaining fibers of about 30%.

The density of distribution of nerve fibers in the experimental animals was 28.2 ± 1.5% greater than in control 2, and it was also higher than in control 1, i.e., in intact rabbits (Fig. 2). Meanwhile the intensity of luminescence of the varicose expansions in most cases showed opposite changes, whereas in the adrenergic plexuses of the basilar and middle cerebral arteries it showed a tendency to decrease. The maximal value of the decrease in luminescence in the basilar artery relative to control 2 was 34.2 ± 3.3%, and in the middle cerebral artery 31.6 ± 1.9%. A similar phenomenon also was observed in the nerve plexuses of the pial vessels in the territory supplied by the basilar artery (Table 1).

Stimulation of NLC thus leads to redistribution of catecholamines in nerve fibers and endings composing the intramural plexuses of the basilar and cerebral arteries, as is shown by increased activity of an additional number of adrenergic nerve structures of all the blood

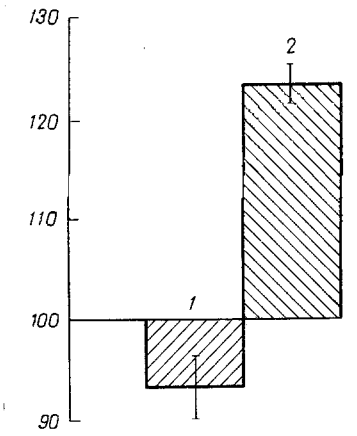

Fig. 2. Density of distribution of adrenergic nerve fibers in plexuses of basilar and cerebral arteries (in %) of rabbits with implanted electrodes (1) and experimental animals (2).

TABLE 1. Changes in Intensity of Luminescence of Adrenergic Nerve Fibers in Response to Stimulation of NLC

Test object	Decrease	Increase	Differences not significant
Basilar artery	4	1	1
Posterior cerebral artery	3	2	1
Middle cerebral artery	5	—	1
Anterior cerebral artery	1	2	2
Pial vessels	4	—	3

Legend. Numbers indicate number of animals.

vessels studied, associated with a decrease in the specific content of mediator in the fibers of the basilar and middle cerebral arteries. The results shed light on the mechanism of the constrictor response, described in the literature, recorded as changes in the systemic arterial pressure and total cerebral blood flow during electrical stimulation of NLC [1, 6]. The effects described in the publications cited above do not depend on desympathization, so that the reactive changes in the nervous apparatus of the cerebral vessels investigated can be linked with direct influences from NLC. Information on the dynamics of the catecholamine concentration in nerve fibers in different parts of the circle of Willis at the base of the brain is particularly interesting. For instance, a decrease in the specific content of catecholamines in fibers of the basilar and middle cerebral arteries enables the cause of the increase in the local blood flow in the parietal cortex and hypothalamus against the background of integral constriction of the vascular bed of the brain in response to stimulation of NLC and structures adjacent to them, to be explained [1, 12]. A similar, although weaker tendency also is found in the nervous apparatus of the pial vessels in the territory of distribution of the basilar artery. It can be tentatively suggested that the redistribution of catecholamines demonstrated by the writers is a manifestation of a unique kind of compensatory reaction, which partially or completely masks the constrictor effect of stimulation of NLC, which has led some workers to deny that the latter has a role in the regulation of the intracranial hemodynamics [9]. The agreement between our own results and the biochemical data indicating changes in the catecholamine content in the corresponding brain regions during stimulation of NLC [8] is worthy of attention. As a result of this, the changes discovered in this investigation can be linked with local vascular responses.

LITERATURE CITED

1. T. V. Balueva, Fiziol. Zh. SSSR, 69, No. 7, 913 (1983).
2. Yu. E. Moskalenko, Textbook of Physiology. Physiology of the Circulation; Physiology of the Vascular System [in Russian], Leningrad (1984), pp. 352-381.
3. P. A. Motavkin and V. M. Chertok, Histophysiology of Vascular Mechanisms of the Cerebral Circulation [in Russian], Moscow (1980).
4. A. P. Pugovkin and K. G. Tayushev, Vopr. Neirokhir., No. 4, 54 (1985).
5. R. A. Stropus, "Cholinergic and adrenergic innervation of the heart and its changes in cardiovascular pathology," Author's Abstract of Dissertation for the Degree of Doctor of Medical Sciences, Moscow (1982).
6. S. I. Teplov, Neurogenic Control of the Blood Supply of the Heart and Brain [in Russian], Leningrad (1980).
7. V. M. Ugryumov, S. I. Teplov, and G. S. Tigliev, Regulation of the Cerebral Circulation [in Russian], Leningrad (1984).
8. D. Bates, R. M. Weinshilboum, R. J. Campbell, et al., Brain Res., 136, 431 (1977).
9. N. Dahlgren, O. Lindvall, T. Sakabe, et al., Brain Res., 129, 11 (1977).
10. L. Edvinsson, Acta Physiol. Scand., 96, Suppl. 427, 1 (1975).
11. J. Katayama, J. Ueno, T. Tsukiyama, et al., Brain Res., 216, 173 (1981).
12. C. Mitchell, D. Mitchell, and C. Rosendorff, Cardiovasc. Res., 12, 42 (1978).
13. M. E. Raichle, J. O. Eichling, R. L. Crubb, et al., Dynamics of Brain Edema, Berlin (1976), pp. 381-384.
14. J. C. Torre, Brain Res., 136, 443 (1977).
15. J. Trakura, K. Vamamoto, M. Tonyama, et al., Stroke, 8, 360 (1977).

ACTION OF DEXTRAN-MODIFIED HYALURONIDASE IN EXPERIMENTAL SILICOSIS

O. G. Arkhipova, V. V. Yaglov,
A. V. Maksimenko, L. V. Pavlovskaya,
O. Yu. Konovalova, E. A. Varsanovich,
L. M. Bezrukavnikova, V. I. Fedorova,
V. N. Fedorova, and V. P. Torchilin

UDC 616.24-003.662-092.9-085.355:
[577.152.429].015.2:615.384

KEY WORDS: experimental silicosis; modified hyaluronidase; dextran; inhalation; enzyme therapy.

Silicosis is an occupational disease that develops through exposure to industrial aerosols containing quartz. The treatment of silicosis is an important problem in occupational medicine. Theoretical, clinical, and experimental data [1-3,5] relating to the search for agents with which to treat silicosis show that as yet no sufficiently effective remedies free from side effects have been found. During the development of fibrosis of the lungs under the influence of dust, synthesis of collagen and proteoglycans and the formation of collagen fibrils are stimulated. Proteoglycans form intermolecular bonds in collagen, regulate fibrillogenesis, and give the collagen fibers their stability [8]. Hyaluronidase (EC 3.2.1.35) depolymerizes glycosaminoglycans [4], and this may lead to regression of fibrosis. Many years of experience of the use of native hyaluronidase in clinical practice has shown that the enzyme is effective only if applied locally [4]. On parenteral administration its activity is low, evidently because the body contains many inhibitors. Attempts have been made to increase the stability of the enzyme under physiological conditions by covalent binding to N-hydroxypolyethylenepiperidine [6]. However, because of the toxicity of the matrix, this preparation

Laboratory of Biochemistry, Clinical Toxicology, and Chemotherapy, and Laboratory of Pathomorphology, Research Institute of Work Hygiene and Occupational Diseases, Academy of Medical Sciences of the USSR. Laboratory of Engineering Enzymology, Institute of Experimental Cardiology, All-Union Cardiologic Scientific Center, Academy of Medical Sciences of the USSR, Moscow. (Presented by Academician of the Academy of Medical Sciences of the USSR V. N. Smirnov.)
Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 103, No. 2, pp. 221-223, February, 1987. Original article submitted January 30, 1986.

