CHANGES IN THE MORPHOLOGY AND FUNCTIONAL STATE OF THE CAPILLARY SYSTEM OF THE CAT CEREBRAL CORTEX IN RESPONSE TO ADRENERGIC AGENTS DURING INHIBITION OF PROSTAGLANDIN BIOSYNTHESIS

É. S. Gabrielyan, R. Sh. Matevosyan, and É. A. Amroyan

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Data collected in the last decade provide evidence of the modulating role of prostaglandins (PG) in adrenergic transmission, with a negative feedback type of mechanism in different organs [5, 6].

The object of the present investigation was to study the morphological and functional state of the capillary system of the cerebral cortex in response to injection of noradrenalin (NA) and stimulation of the cervical sympathetic nerve in control cats and during inhibition of PG biosynthesis by indomethacin.

EXPERIMENTAL METHOD

Experiments were carried out on 32 cats anesthetized with pentobarbital (25 mg/kg). Noradrenalin (from Lederle, USA) was injected into the carotid artery in a dose of 5 μg/kg. Indomethacin (from Polfa, Poland) dissolved by Palmer's method [11], was injected by intravenous infusion from an automatic syringe (Perfusor E, from Hugo Sachs Elektronik) in a dose of 2 mg/ml over a period of 1 min. After isolation of the cervical sympathetic nerve it was stimulated by an electric current with a frequency of 5 Hz and voltage 7 V for periods of 10 msec in the course of 20 sec. Material for investigation was collected through a burr-hole in the frontal region of the skull. Pieces of brain measuring 1 mm^3 were fixed in 5% formalin and subsequently treated by a new invasive method of demonstrating the intramural microcirculation [4], based on direct staining of the vessel walls. The diameter of functioning capillaries (over 4 μ) was determined in microscopic specimens by means of an ocular micrometer and the number of sharply constricted capillaries (under 4 μ) in 100 fields of vision also was calculated. The significance of the differences between data for the experimental and control groups was assessed by the Fisher–Student test.

EXPERIMENTAL RESULTS

In the experiments of series I the state of the cortical capillary system in the control animals and its response to injection of NA were studied. The mean diameter of the capillaries in the control cats (six animals) was 6.6 μ and the number of sharply constricted capillaries, calculated per 100 fields of vision, was 12 (Table 1). It should be noted that among the sharply constricted capillaries, permeable only to plasma, mainly vessels 3-4 μ in diameter were observed, and only very rarely capillaries with a diameter of 2 μ; capillaries 1 μ in diameter or completely closed were not found. The diameter of the capillaries increased somewhat (by 11.07%) 50 sec after injection of NA (seven cats), but the number of sharply constricted capillaries more than doubled.

During inhibition of PG biosynthesis by indomethacin (six cats) the vasoconstrictor action of NA was more clearly manifested. For instance, the diameter of the capillaries was reduced statistically significantly by 16.4% compared with its initial value in control cats; the number of sharply constricted capillaries increased at the same time by 2.7 times.

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The effect of stimulation of the cervical sympathetic nerve on the state of the capillary system of the cerebral cortex was studied in the experiments of series II (four cats). Sympathetic nerve stimulation led to a decrease in the diameter of the capillaries by 18.7% and an increase in the number of sharply constricted capillaries by 2.4 times (Table 1).

During inhibition of PG biosynthesis by indomethacin (four cats) sympathetic nerve stimulation revealed an even greater increase in the number of sharply constricted capillaries (by 2.7 times), but the diameter of the capillaries was virtually unchanged.

To make sure that the changes observed under the influence of adrenergic agents during inhibition of PG biosynthesis did not conceal certain effects of indomethacin, the effect of indomethacin alone was studied in a separate series of experiments (five cats). As Table 1 shows, this caused no marked changes in the state of the cerebral cortical capillary network compared with the control.

Despite the numerous investigations conducted in recent years, the problem of adrenergic regulation of the cerebral circulation has lost none of its urgency. The results now obtained suggest that the influence of the adrenergic component is clearly expressed at the cerebral capillary level.

Effects of sympathetic nerve stimulation and of exogenous NA on the cerebral cortical microcirculation are due more to a decrease in the number of actively functioning capillaries than to a change in their diameter. This fact is evidence that precapillary sphincters are more susceptible to the action of exogenous and endogenous NA. The number of active capillaries is known to be determined by the state of the precapillary sphincters, which are linked by the negative feedback principle with tissue metabolites [3]. The role of the adrenergic component in these reciprocal interactions evidently consists of maintaining the tone of the precapillary sphincters at a level adequate to meet the demands of the blood supply, at the cerebral cortical microcirculation level.

The ability of exogenous and endogenous NA to reduce the diameter of the cortical capillaries is interesting on its own account. It seems there are two possible explanations of this phenomenon. The first is that the change in the diameter of the capillaries under the influence of sympathetic stimulation and NA is passive in character and is the result of hemodynamic changes, taking place mainly in the precapillary sector, where both muscle and nerve cells responding actively to adrenergic influences are represented. A no less important role may also be played by changes in the precapillary space. However, as A. M. Chernukh [3] rightly points out, this mechanism cannot open closed capillaries. The second explanation assumes the possibility of a direct effect of adrenergic influences on cerebral capillaries, i.e., ability of the capillaries to change their diameter actively. Most investigators consider that capillaries are unable to dilate or constrict actively [9]. However, as long ago as in 1927, Krogh [2] expressed the view that capillaries can change their diameter actively because of the contractile power of the pericytes and because of swelling and shrinking of the endothelium. Comparatively recently [12] it was shown by electron-microscopic investigations that the brain capillaries are innervated by unmyelinated nerve endings, possibly adrenergic in nature. Investigations by the use of immunofluorescence analysis revealed the presence of contractile proteins (actin and myosin) in the pericytes and endothelial cells of the cerebral capillaries [10]. These facts suggest that an active change of the lumen of the brain capillaries can occur in response to adrenergic influences.

During inhibition of PG biosynthesis by indomethacin the sensitivity of the microcirculatory system to NA is increased, leading to an increase in the number of nonfunctioning capillaries and to some reduction in their diameter. In experiments with sympathetic nerve stimulation, by contrast with experiments with NA, the diameter of the capillaries did not change significantly but the number of sharply constricted capillaries increased somewhat.

It can be concluded from data obtained by the writers previously [1, 7] that higher concentrations of indomethacin, capable of inhibiting PG biosynthesis at the synaptic level, are needed in order to significantly increase the effect of sympathetic nerve stimulation; consequently, indomethacin potentiates the action of exogenous NA more effectively than that of endogenous NA on the cerebral vessels.

It can thus be accepted that the effect of exogenous and endogenous NA on the microcirculation in the cerebral cortex depends to a certain degree on endogenous PG biosynthesis, inhibition of which may lead to potentiation of adrenergic effects, creating a hazard of development of cerebrovascular spasm. From this point of view it is difficult to overestimate the

TABLE 1. Effect of Noradrenalin and Stimulation of Cervical Sympathetic Nerve on Morphology and Functional State of Cerebral Cortical Capillaries of Cats before and during Inhibition of PG Biosynthesis (M ± m)

Experimental conditions	No. of animals	Mean diameter of capillaries, μ	No. of sharply constricted capillaries, mean per 100 fields of vision
Control	6	6,60±0,05	12,00±0,75
NA (5 μg/kg by intracarotid injection)	7	5,87±0,18 $P<0,001$	25,00±2,47 $P<0,001$
NA preceded by indomethacin (2 mg/ml during 1 min, intravenously)	6	5,52±0,13 $P<0,001$	33,00±0,46 $P<0,001$
Stimulation of sympathetic nerve	4	5,37±0,27 $P<0,001$	29,0±1,4 $P<0,001$
Stimulation of sympathetic nerve after indomethacin	4	5,43±0,18 $P<0,05$	32,0±1,4 $P<0,001$
Indomethacin (2 mg/ml during 1 min, intravenously)	5	6,54±0,33	12,00±0,89

importance of PG, which play the role of physiological antagonists of NA [7, 8], and this is further confirmation of results which the writers obtained at the level of the microcirculation of the cat brain.

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