EFFECT OF LOWERING OF THE HYDRODYNAMIC RESISTANCE OF FLUID ON RESPONSES OF THE CEREBRAL ARTERIES DURING PERFUSION

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UDC 616.133.33-018.7-005-07-092.4

KEY WORDS: isolated arteries; endothelium-dependent reactions; linear high-molecular-weight polymers; autoregulation of the cerebral blood flow.

Introduction of special linear high-molecular-weight polymers in low concentrations into the bloodstream of various experimental animals (10^{-7}-10^{-5} g/ml circulating blood), causing reduction of the hydrodynamic resistance of the blood, leads to sufficiently long-lasting changes in certain parameters of the systemic hemodynamics, expressed as lowering of the systemic blood pressure (SBP), lowering of the total peripheral resistance (TPR), and an increase in the cardiac output (CO) [4, 7, 9, 10]. Under these circumstances an autoregulatory reaction of constriction of the pial arteries is observed, not the ordinary response of their dilatation to a fall of SBP [3]. The conclusion regarding the autoregulatory character of this response was drawn from the fact that only vasoconstriction of the pial arteries enables the cerebral blood flow (CBF) to be maintained at a steady level during the development of an increased CO and blood flow in the large arteries.

If reduction of the hydrodynamic resistance of the blood, according to data in the literature, takes place only when special polymers with unbranched molecular structure and with extraordinary length (of the order of 100 μm) are used, it can be tentatively suggested that solutions of these polymers will not only reduce the pseudotubulization of the blood flow and thereby reduce the nonsteady-state of its course, but they will also change the relations between the vascular wall and the blood flow. The problem of the mechanism of sensitivity of the cerebral vessels to a change in character of the blood flow at constant volume of CBF has not yet been studied.

The aim of this investigation was to discover whether vasoconstrictor reactions to perfusion of the isolated arteries with liquids with added solutions of polymers take place, whether they depend on the conditions of perfusion, and whether they are endothelium-dependent.

EXPERIMENTAL METHOD

The functional state of the blood vessels was studied by two methods. The first envisaged perfusion of a vascular segment and parallel recording of the perfusion pressure and diameter of the vessel [2]. The experimental system used enables a vessel to be perfused under close to real conditions, and the rate of perfusion and the perfusion pressure to be varied within wide limits, and if necessary, the perfusion to be carried out at a stabilized rate. The diameter of the vessel was measured by means of a system which recorded it by an optical method (275 K model, HSE, East Germany). De-endothelization of the vessel was carried out directly on the apparatus by means of a jet of air. The second method enabled the contractile activity of a spiral strip of the vessel to be investigated under isotonic conditions, by means of a model HS transducer (West Germany). The investigation was conducted on six segments and five spiral strips of the carotid artery of six cats and four segments of the middle cerebral arteries of the human brain, obtained from cadavers of persons dying accidentally (not more than 3 h after death).

Laboratory of Experimental Pathology of the Nervous System, Research Institute of Neurology, Academy of Medical Sciences of the USSR, Moscow. Laboratory of Pharmacology of the Circulation, Central Research Laboratory, Erevan Medical Institute. (Presented by Academician of the Academy of Medical Sciences of the USSR B. I. Tkachenko.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 110, No. 9, pp. 238-240, September, 1990. Original article submitted December 30, 1989.

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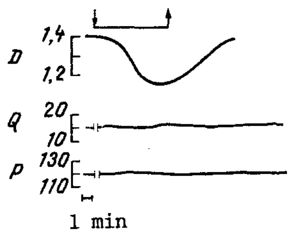


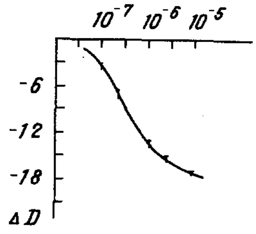


Fig. 1 Fig. 2

Fig. 1. Decrease of diameter (D, mm) of a segment of cat carotid artery under conditions of stabilized volume (Q, ml/min) and pressure (P, mm Hg) of perfusion and during injection of polyethylene oxide ($2 \cdot 10^{-6}$ g/ml) into perfusion fluid. Arrows indicate beginning and end of infusion of polymer.

Fig. 2. Effect of various concentrations of polymer (abscissa, g/ml) on reduction of diameter of perfused segment of cat carotid artery (ordinate, %).

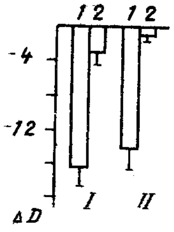
The polymer used to reduce the hydrodynamic resistance of the liquid was polyethylene oxide (Polyox) WSR-301 (Union Carbide, USA). Concentration of Polyox solutions of 10^{-8} to 10^{-4} g/ml were used, with a perfusion pressure of the order of 110-120 mm Hg and constant delivery at the rate of 15 ml/min. In the experiments in which the flow rate was varied, this took place between 15 and 40 ml/min.

EXPERIMENTAL RESULTS

Under conditions of stabilized perfusion of the isolated vessels with a solution of the polymer in a concentration of 10^{-5}-$2 \cdot 10^{-6}$ g/ml a vasoconstrictor reaction occurred (Fig. 1). After cessation of infusion of the vessels with the solution containing Polyox, their diameter returned to its initial value. Thus the same vasoconstrictor response was reproduced on the isolated vessels as the response of the pial arteries which we described to intravenous injection of corresponding amounts of a solution of the polymer [3]. The response of the isolated arteries was dose-dependent and developed starting with a concentration of the polymer of 10^{-7} g/ml. With a concentration of the polymer of 10^{-5} g/ml the effectiveness of the solutions began to diminish, i.e., both in the experiments in vitro and in those on animals, concentrations of $2 \cdot 10^{-6}$-10^{-6} g/ml were most effective, reducing the lumen of the arteries by 15-18%. The same response was observed in all investigations, but no strict explanation of it is forthcoming (Fig. 2).

The appearance of this response indicates that the solution of the polymer can influence the smooth muscles of arteries, but the active vascular response arises only during perfusion of the vessels by solutions of the polymer. Addition of the polymer in the same concentrations to the bath containing the spiral strip of blood vessel caused no vascular response. It can accordingly be concluded that solutions of the polymer as such have no direct vasoconstrictor action.

After de-endothelization of segments of the cat carotid artery and human middle cerebral artery the vasoconstrictor effect on perfusion of the solution of the polymer disappeared (Fig. 3), and it was accordingly concluded that this vasoconstriction is epithelium-dependent. An increase in the flow rate of perfusion of the vascular segment from 15 to 40 ml/min under constant perfusion pressure evoked a smaller vascular reaction to addition of a solution of the polymer (10^{-6} g/ml) to the perfusion fluid (Fig. 4). In our view, this phenomenon can be explained by moderation of the deformation of the vascular endothelium during an increase in the perfusion flow rate in the presence of the polymer. In fact, solutions of these polymers are able to reduce the hydrodynamic resistance of liquids, because of reduction of the pseudo-turbulization of their flows (during a nonturbulent type of course), in accordance with the so-called Toms effect [5].



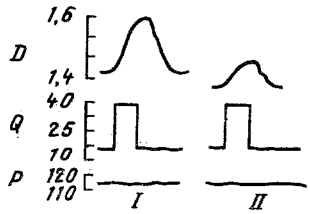


Fig. 3 Fig. 4

Fig. 3. Effect of solution of polyethylene oxide ($2 \cdot 10^{-6}$ g/ml) on diameter of vascular segments of perfused cat carotid artery (I) and human middle cerebral artery (II) before (1) and after (2) de-endothelization.

Fig. 4. Response of vascular segment of cat carotid artery to increase in perfusion flow rate (Q, ml/min), under constant perfusion pressure (P, mm Hg) before (I) and after (II) addition of polyethylene oxide solution to perfusion fluid (10^{-6} g/ml).

Experiments with perfusion of isolated blood vessels with liquid containing added special polymers thus showed that the vessels are sensitive to a change in the character of flow, as it were to its "untidiness"; this response, moreover, appears not only in animals but also in vitro, and it is endothelium-dependent. The investigation also showed that a vasoconstricting endothelium-dependent reaction is possible, a fact which substantially modifies existing views on the presence of a normal vasodilator endothelium-dependent vascular response. On the basis of these results the mechanism of this response can be regarded to be as follows. We know that liquid moving along a vessel creates a shear stress in its wall, a change in which affects the tone and diameter of the vessels. Some workers [8] link the vascular response purely with a change in the linear flow rate of the fluid and/or its viscosity, for it is the linear velocity and viscosity of the fluid that determine the shear stress created on the endothelial surface. Within certain limits, dependence between these values is unchanged, provided that no external force modifies the hydrodynamics of flow of the liquid, as was the case in the experiments in [1, 6, 8]. The concentrations of the solutions of the polymer which we used did not change the viscosity of the fluids [3], and for that reason this value can be disregarded. Thus if the responses of vessels perfused in the presence of polymers be explained strictly from the standpoint of V. M. Khayutin's concept, this would necessitate assuming that solutions of these polymers reduce shear stress through the flow rate of the liquid, which is not observed in experiments in which solutions of these polymers are used. Under the conditions of a nonturbulent flow of liquids reduction of their hydrodynamic resistance can be brought about but not through changes in its velocity profile, which is unchanged [5]. This effect in laminar flows is due entirely to a decrease in the possible local perturbations at irregularities of the surface of the vessel walls during pulsating movement of blood at sites of bends and branchings, i.e., a decrease in the hydrodynamic resistance of these liquids takes place only in accordance with the Toms effect, and not strictly according to its rules. Thus to explain the vasoconstrictor effect appearing during perfusion with solutions of polymers, it is necessary to examine the shear stress on the wall of the vessel as a function not only of the linear flow rate, but also of the interrelations between the marginal flow and irregularities of the endothelial surface, on which secondary whorls and stagnant currents are possible. In the presence of the polymer (Fig. 4) the increase in the linear flow rate was accompanied by a less marked dilatation response, i.e., dependence of shear stress on linear flow rate was modified in this case. In our view this is connected with moderation of the degree of local perturbations of flow on the endothelial surface, reducing the shear stress on the vessel wall.

Thus it must be emphasized that the purely physical affects the polymer, namely reduction of the hydrodynamic resistance of flow on account of diminution of its pseudoturbulization, ought to lead to physiological responses of the arteries on account of a change in relations between the vessel wall and the blood flow. Taking into account the above considerations, we deem it necessary to extend our ideas on relations between linear flow rate and shear stress on the vessel wall, for in our experiments an equal increase in the linear flow rate led to different changes in diameter of the vessel.

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COMPARISON OF EPILEPTIC SYNDROMES INDUCED BY LIMBIC ELECTRICAL STIMULATION (KINDLING) WITH 24-48-HOUR AND 5-MINUTE INTERVALS

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UDC 616.853-008.6-092.9:612.014.424]-07

KEY WORDS: rapid and classical kindling; severity of seizures; electroencephalography

A phenomenon of rapid kindling has recently been obtained [2, 4, 9], in which a generalized seizure syndrome develops in animals in the course of a few hours in response to electrical stimulation (ES) of the brain with an interval of 3-5 min, instead of the 24-48-h interval used in classical kindling [7]. The present writer showed [4] that one particular feature of rapid kindling is significant and long-lasting inhibition of the postictal refractory period (PIRP). In the course of classical kindling, simultaneously with progression of epileptic responses, antiepileptic responses also are intensified [8, 12, 13]. PRIP in these animals lasts several times longer than in intact animals [11], but during bilateral ES of the amygdala, PIRP lasts even longer than during unilateral stimulation [10]. The following questions accordingly arise: do epileptic reactions differ in animals subjected to classical kindling, and if so, what is the nature of this difference. The investigation described below was undertaken to study these problems.

EXPERIMENTAL METHOD

Experiments were carried out on 34 chinchilla rabbits weighing 2.5-3 kg. Electrodes (nichrome wire 100 μ in diameter) were implanted bilaterally into the sensomotor and occipital zones of the cortex, dorsal hippocampus, and amygdaloid and caudate nuclei bilaterally 2 weeks before the experiment.

The animals were divided into four groups.

Moscow. (Presented by Academician of the Academy of Medical Sciences of the USSR G. N. Kryzhanovskii.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 110, No. 9, pp. 240-242, September, 1990. Original article submitted June 23, 1989.

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