F-actin with myosin is disturbed [15]. Staphylococcal toxin disturbs the contractile power of actomyosin of smooth muscles [10]. The action of TT is probably similar to the action of these poisons. The results described above indicate that the contractile proteins of nerve endings, responsible for exocytosis of mediators, are the probable target for TT. The immediate target for TT is probably the ALP built into the presynaptic membrane. The result of binding of TT and ALP is blocking of contact of SV with the presynaptic membrane and of mediator secretion. It is not yet clear whether the TT molecule penetrates through the membrane of nerve endings or whether it acts on the cytoskeletal network and on SV in the cytosol of nerve endings.

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PATHOGENESIS OF EXPERIMENTAL CEREBRAL HEMORRHAGE DURING HYPERTENSION IN THE LIGHT OF MICROCIRCULATION STUDIES

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KEY WORDS: brain; pathogenesis; hemorrhage; microcirculation.

Problems concerning with the pathogenesis of cerebral hemorrhage in hypertension have recently been examined in the light of microcirculation studies [1, 3].

Microcirculation problems include not only the principles of transcapillary exchange and the structure and ultrastructure of the walls of the microvessels, but also the state of the blood itself [10]. It is accordingly interesting to study the morphology of the microcirculation and indices of blood clotting and fibrinolysis in the early stages of experimental hemorrhages which, by their neurohumoral mechanisms, have features of similarity with hemorrhages due to apoplexy in man. Audiogenic apoplexy, excluding the possibility of limiting inhibition [5], and improved by the author [2] by the addition of hypoxic hypoxia, was used as the model of cerebral hemorrhage associated with hypertension.

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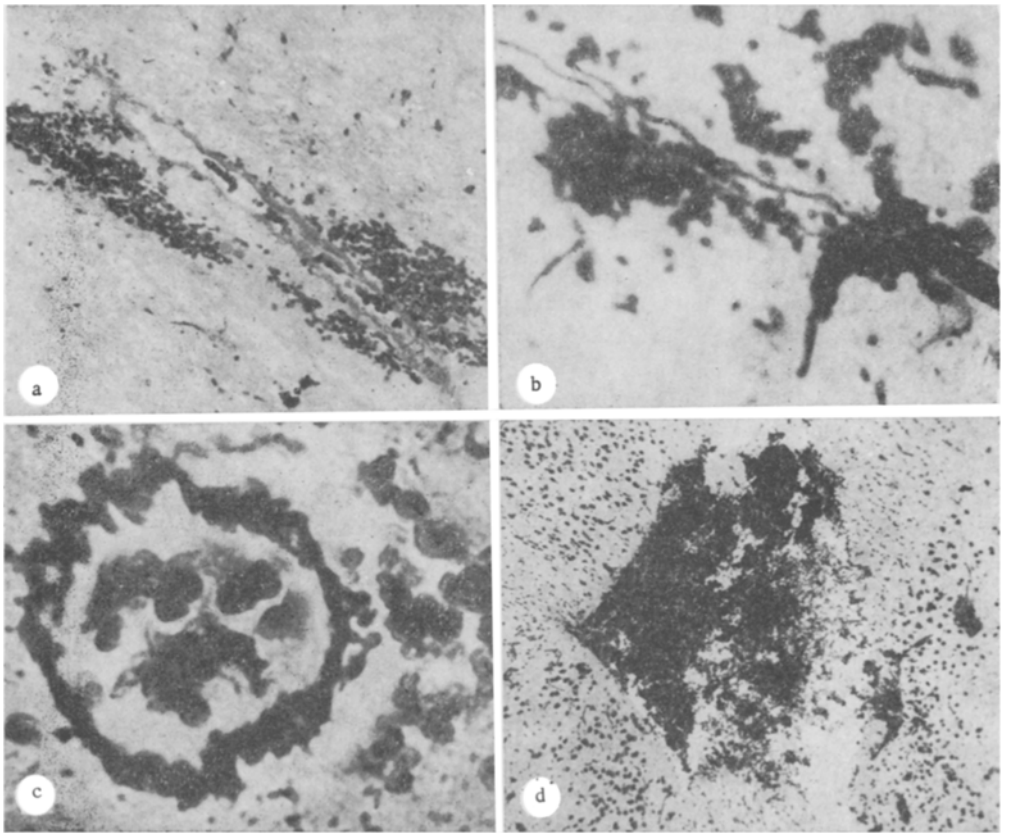

Fig. 1. Experimental hemorrhages in brain substance. a) Concentrations of erythrocytes around arteriole with signs of dystonia. Stained with fuchsine-aniline orange by Mallory's method, 200×; b) concentrations of erythrocytes around capillary. Heidenhain's iron-hematoxylin, 200×; c) hyperargyrophilia of wall of arteriole in zone of hemorrhage. Impregnation with silver nitrate by Wilder's method, 200×; d) hemorrhage with destruction of brain substance. Heidenhain's iron-hematoxylin, 80×.

EXPERIMENTAL METHOD

Experiments were carried out on 24 male albino rats weighing 180-250 g, which were exposed to continuous sound with an intensity of 120 dB, in a chamber with a capacity of 2000 cm^3, in accordance with the scheme in [6]. The animals were then exposed for 6 h to hypoxic hypoxia in the SBK-48M pressure chamber, where the atmospheric pressure was maintained at a level corresponding to an altitude of 7500 m. Half of the animals were decapitated immediately after the experiment, the rest 24 h later. Fifteen intact rats served as the control. The blood escaping at decapitation was collected for electrocoagulography in order to determine the beginning (T_1), end (T_2), and duration of its coagulability (T), and also the beginning of clot retraction and fibrinolysis (T_3). The state of the sympathico-adrenal system was assessed by determining the daily excretion of catecholamines by a fluorometric method. The blood pressure was measured in the caudal artery.

After fixation in 10% neutral formalin solution the brain was embedded in paraffin wax. Sections through the cerebral hemispheres were stained with hematoxylin and eosin, with fuchsine and aniline orange by Mallory's method, with Heidenhain's iron-hematoxylin, with picrofuchsine by Van Gieson's method, and impregnated with silver nitrate by Wilder's method. Over the whole area of the section the diameter of the lumen of the arterioles and venules in the brain substance was measured by an ocular micrometer. Microvessels with a single layer of smooth muscle cells were taken to be arterioles [8]. Microvessels over 30 μ in diameter, without muscle cells, were regarded as venules [7]. The number of functioning capillaries and the number of hemorrhages were counted in 10 fields of vision of the microscope and the area of the hemorrhages was calculated. The statistical analysis of the data was carried out by Montsevichute-Éringene's method, using Student's tables.

EXPERIMENTAL RESULTS

In animals exposed to the action of the acoustic stimulus and hypoxia, immediately after the experiment marked activation of blood clotting ($T = 31.6 \pm 4.8$ sec, compared with 44.0 ± 2.1 sec in the control) and fibrinolysis was found ($T_3 = 271.0 \pm 28.9$ sec compared with 455.0 ± 44.4 sec in the control). After 24 h, the coagulability of the blood returned to normal ($T = 43.0 \pm 4.8$ sec), but fibrinolysis remained at the previous level ($T_3 = 273.0 \pm 39.9$ sec). The catecholamine content in the 24-hourly sample of urine from the experimental animals was sharply increased (5.75 ± 0.65 μg compared with 0.6 ± 0.02 μg in the control), mainly on account of adrenalin (3.75 ± 0.7 μg/24 h). The blood pressure of the experimental animals was raised on average to 155 mm Hg compared with 95 mm Hg before the experiment.

The diameter of the lumen of the brain arterioles immediately after the experiment was increased to 16.2 ± 1.2 μ (compared with 12.2 ± 1.1 μ in the control) and it remained at that level 24 h later. The diameter of the venules also was considerably increased both immediately after the experiment (43.3 ± 1.4 μ) and also 24 h later (42.2 ± 1.6 μ compared with 33.0 ± 1.1 μ in the control). The number of functioning capillaries per field of vision of the microscope increased sharply both immediately after the experiment (20.1 ± 1.2) and also 24 h later (24.3 ± 1.4 compared with 11.3 ± 0.5 in the control).

Besides dilatation of the vessels, dystonia of their walls and hemorrhages also were observed. Signs of stasis were frequently seen in the venules. The number of hemorrhages per section through the cerebral hemisphere averaged 22.4 and their area was 922.5 μ^2, whereas in the control animals only solitary small perivascular concentrations of erythrocytes were found. Some hemorrhages were located around the arterioles, venules, and capillaries, without injuring the nerve tissue (Fig. 1). Sometimes the blood penetrated into and destroyed the brain substance (Fig. 1d). In the region of the hemorrhages the argyrophilic fibers in the vessel walls sometimes merged and were intensively impregnated with silver nitrate (Fig. 1c), sometimes more loosely arranged and fragmented. Outside the zone of hemorrhages no changes were found in the argyrophilic skeleton of the vessels. The model thus enabled some light to be shed on certain aspects of the pathogenesis of experimental hemorrhages associated with hypertension. In particular, these hemorrhages were shown to develop against the background of activation of fibrinolysis, which persisted after normalization of the coagulability of the blood, i.e., against the background of disturbance of the defensive-adaptive mechanisms [9], evidently attributable to overexcitation of the sympathico-adrenal system.

Stimulation of the autonomic nervous system, caused in these experiments by combined exposure to sound and hypoxia, leads to hypertension. However, instead of the usual response to hypertension in the form of constriction of the arterioles in the brain substance, the arterioles dilate, reflecting the failure of autoregulation of the cerebral circulation [4, 11, 12]. The increase in the lumen of the arterioles, i.e., the increase in the volume blood flow, leads to considerable congestion of the capillaries. These disturbances of the microcirculation are aggravated by the consequences of venous congestion, in the form of stasis, and also by activation of fibrinolysis, which ultimately leads to the development of diapedesis of the erythrocytes from arterioles, venules, and capillaries.

The study of the ultrastructure of the various components of the microcirculatory system before and in the various phases of development of diapedesis is naturally of the greatest interest. The models described can be used for this purpose, for in nearly every section of the cerebral hemisphere the early stages of hemorrhages can be observed and their study provides additional information on their pathogenesis in connection with changes in the microcirculation.

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EFFECT OF FEVER ON REACTIVITY OF THE ADRENAL CORTEX

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KEY WORDS: fever; pyrogens; adrenal cortex.

When introduced into the body, bacterial pyrogens are known to activate the pituitary-adrenal system [1-3, 5-7]. However, this fact cannot be regarded as undisputed proof of the interdependence of pyrexial and glucocorticoid reactions, for fever, if produced by leukocytic pyrogen, freed to some degree from balanced substances, and a more adequate stimulus for the organism, is not accompanied by the hormonal response described above [3]. These and other data are evidence that activation of the adrenal cortex in response to administration of bacterial pyrogens and also of native (unpurified) leukocytic pyrogen is unconnected with elevation of the body temperature. The absence of any strict parallel between the pyrexial reaction and the response of the pituitary-adrenal system also indicates that the mechanisms triggering them are relatively independent. Nevertheless, this does not rule out the possibility that a febrile reaction may affect the functional state and reactivity of the adrenal cortex. The study of this problem is of great interest from both theoretical and practical points of view, if the clinical use of pyrogenic agents is taken into account.

The object of this investigation was to study the effect of fever on the reactivity of the adrenal cortex following administration of its natural stimulator, adrenocorticotrophic hormone (ACTH).

EXPERIMENTAL METHOD

Male rabbits were used. The reaction of the adrenal cortex was assessed by measuring changes in the 11-hydroxycorticosteroid (11-HCS) concentration in peripheral blood plasma by the method of Usvatova and Pankov [4] in response to intravenous injection of ACTH. Pyrogenal or leukocytic pyrogen (both native and after partial alcoholic purification – the low-molecular-weight specific pyrogenically active fraction) were used as pyrogens. Pyrogenal was injected intravenously in a dose of two minimal pyrogenic doses (MPD) per kg and leukocytic pyrogen also was injected intravenously (at once or by the drip method) in a dose of 1.5 ml/kg. For intravenous drop injection of leukocytic pyrogen at the rate of 1 ml/h, a polyethylene catheter was fixed in the rabbit's auricular vein. Pyrogen-free physiological saline was injected into control animals under similar conditions. The rectal temperature was measured at a depth of 4 cm by means of a fixed transducer connected to an electrothermometer, every 30 min during the first 2 h of the experiment, and subsequently every hour. The results were subjected to statistical analysis.

EXPERIMENTAL RESULTS

In the experiments of series I, one-stage intravenous injection of pyrogenal or of native leukocytic pyrogen was used as the pyrogenic agents. The animals developed the ordinary febrile reaction [3], accompanied by elevation of the 11-HCS level on average by 67.1% (pyrogenal) and 57.2% (native leukocytic pyrogen). Injection of ACTH against the background of fever induced by pyrogenal (in the stage of fever and an already

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