DISTURBANCE OF THE CEREBRAL BLOOD FLOW DURING ISCHEMIA AND ITS CORRECTION BY LEU-ENKEPHALIN

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Opioid peptides play a definite role in the central regulation of the circulation [4, 14]. The effect of the opiate receptor agonist Leu-enkephalin (LE) on the work of the cardiovascular system is to reduce BP, the heart rate, sensitivity of the baroreceptor reflex, and the strength of the spastic reactions of the carotid arteries, and to depress neurogenic constrictor responses of the cerebral vessels [4, 7, 8, 11, 13, 14]. The presence of a direct regulatory action of the opioid peptides on neurons of the cardiovascular center in the medulla has been established [5]. Depression of cardiovascular effects of enkephalins by naloxone [4, 5, 14] is evidence that the enkephalinergic system of the brain can modulate the functions of the cardiovascular system. Data obtained by different workers on the effect of LE on the cerebral blood flow are contradictory in character. An increase in the blood flow is observed in the cerebral cortex and hypothalamus by 10 and 7.5% respectively in response to injection of LE (0.03 μg/kg·min) into the main vessels of the brain, and the blood flow in the cortex is reduced by 9% and that in the hypothalamus increased by 5% after intraarterial injection of LE (0.1 μg/kg·min) into rabbits [7]. Under similar experimental conditions intravenous injection of LE (0.1 mg/kg) caused a transient increase in the cerebral blood flow (CBF) in the cortex by 16% followed by a decrease of 28%. The duration of the effect did not exceed 10-15 min [13]. The difference between the reactions can be attributed mainly to differences in the method of administration of the peptide. Data on the effect of LE on the state of CBF under conditions of cerebral ischemia could not be found in the literature.

In recent years yet another important property of LE and its tyrosine-containing analogs was discovered by the present writer: stimulation of the lymphatic flow, both directly through an increase in contractility of the lymphatic microvessels (LMV) which, evidently, possess opiate regulation [9], and also indirectly, as a result of increased permeability of the wall of the blood microvessels by arginine-containing LE analogs (dalargin and its analogs), and intensification of intestinal motor activity [10]. Stimulation of the lymph flow by opioid peptides, which are more effective than the known preparations [3, 6, 15], ought to improve the state of the central hemodynamics and the microcirculation, and in turn, this may be reflected positively in the state of the circulation, including the zone of ischemia.

To test this hypothesis we studied the effect of stimulation of the lymphatic flow by means of LE on the dynamics of CBF on a model of long-term cerebral ischemia.

EXPERIMENTAL METHOD

Experiments were carried out on 105 male albino rats weighing 200-300 g, anesthetized with chloral hydrate (0.6 g/kg, intramuscularly). Cerebral ischemia was induced by bilateral ligation of the common carotid arteries. The local CBF was measured by the hydrogen clearance method in the sensomotor cortex, using the ITK-2M instrument, for 1 h before cerebral ischemia and during 3 h of its course. The microcirculation in the mesentery was studied by biomicroscopy. BP was

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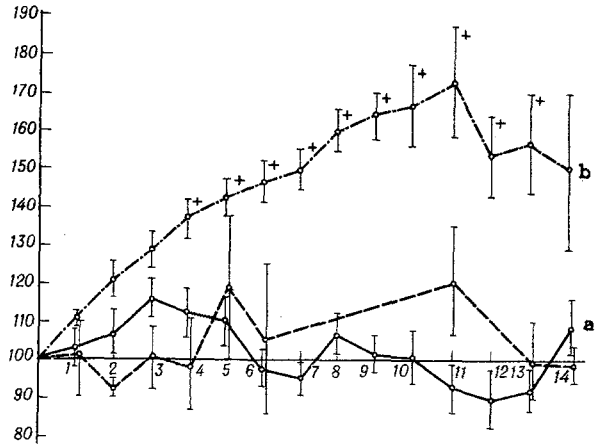

Fig. 1. Local CBV in cerebral cortex of rat in control (a) and after intraperitoneal injection of 1 ml of 0.14 M NaCl (b) and 10 μg/ml LE (c). Abscissa, time intervals (in min); duration of first interval 10 min, second and subsequent intervals 15 min each; ordinate, CBV (in % of initial level, taken as 100). +) Statistically significant differences from control ($p < 0.02$).

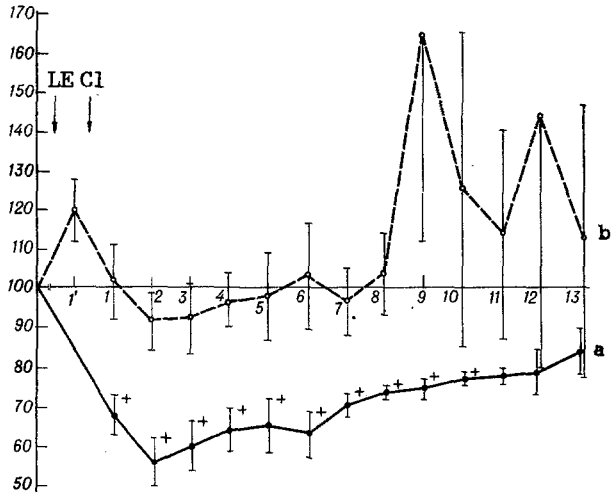

Fig. 2. Effect of prophylactic administration of LE on local CBV in rat cerebral cortex after ligation of common carotid arteries. A) CBV during cerebral ischemia (CI); b) CBV after intraperitoneal injection of 10 μg/ml of LE before CI. Abscissa, time intervals (in min): duration of interval 1' 10 min after injection of LE, of interval 1 10 min after beginning of CI; of interval 2 and subsequent intervals 15 min. Arrows indicate injection of LE and beginning of CI. Remainder of legend as to Fig. 1.

measured by an invasive method in the right femoral and right common carotid arteries, using an electromanometer. To record BP in the carotid sinus, a catheter was introduced cranially into the right common carotid artery and its distal segment was ligated. LE ("Serva," West Germany) was injected intraperitoneally in a dose of 10 μg in 1 ml of 0.14 M NaCl in a dose of 40 μg/kg body weight. There were six series of experiments to study CBF, in series I spontaneous fluctuations of CBF were studied in control animals, in series II the effect of intraperitoneal injection of 1 ml of 0.14 M NaCl was

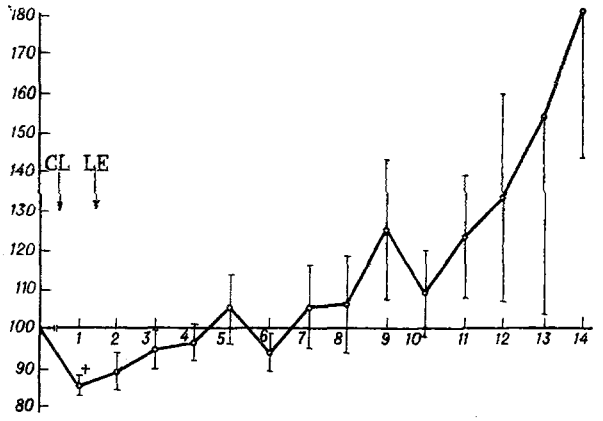

Fig. 3. Effect of therapeutic action of LE on local CBF in rat cerebral cortex after ligation of common carotid arteries. Abscissa, time intervals (in min): duration of first interval 10 min after beginning of ischemia; of second interval 10 min after intraperitoneal injection of 10 μg/ml LE, of third and subsequent intervals, each 15 min. Remainder of legend as to Figs. 1 and 2.

studied, in series III the effect of LE, in IV the effect of cerebral ischemia, in V the results of prophylactic injection of LE 10 min before the beginning of ischemia, and in VI the therapeutic action of LE was studied 10 min after the creation of ischemia. Lymph was collected for 10 min after puncture of the wall of the thoracic lymphatic duct before it emptied into the left venous angle. The rate of lymph formation was calculated in liters/kg/sec. The results were subjected to statistical analysis by computer, with calculation of Student's t.

EXPERIMENTAL RESULTS

In the control animals in a state of general anesthesia (series I) CBV in the cerebral cortex was 54.39 ± 1.42 ml/100 g/min. During the next 3.5 h CBV fluctuated between 90 and 116% compared with the average initial level during the first 40 min of observation, taken as 100% (Fig. 1a). The systemic BP was 98.1 ± 0.3 mm Hg and BP in the sinus was 57.2 ± 1.3 mm Hg. The diameter of the mesenteric arterioles was 14.1 ± 1.45 μ, and of the venules 29.3 ± 3.2 μ. The respiration rate was 71.73 ± 5.03 cycles/min and the pulse rate 300.0 ± 12.5 beats/min. Intraperitoneal injection of 1 ml of 0.14 M NaCl (series II) caused no statistically significant changes in the parameters studied. CBV varied between 92 and 120% compared with the initial level, no different from the control experiments ($p > 0.05$) (Fig. 1b).

Injection of LE (series III) was accompanied by considerable changes in the central and peripheral hemodynamics and the lymphatic circulation. CBV increased progressively to reach higher values (171%) than initially 2.5 h after injection of LE (Fig. 1c). Biphasic changes in BP were observed: reduction by 23% followed by an increase of 8.5%; the heart rate was reduced by 8%; the respiration rate was unchanged. In the intestinal mesentery dilatation of arterioles by 18% and very slight biphasic changes in the lumen of the venules were noted; a reduction of 4% in the diameter followed by an increase by 7.5%. The increase in the velocity of flow of the blood and lymph was noted visually. The greatest changes were found in LMV [8]. The initially noncontracting LMV began to contract intensively with a frequency of 20.3 ± 2.7 contractions/min after a short latent period (7.5 ± 1.8 sec), to reach a maximal frequency of 33 contractions/min. In the control experiments LMV contracted periodically for 5-10 min. LE induced continuous contraction of LMV for 39.5 ± 4.01 min. The increase in rhythmic contractility of LMV is one of the chief factors leading to an increased flow of lymph. The volume of lymph collected from the thoracic lymph duct after injection of LE was increased by 2.6 times compared with initially. In some animals lymph formation was increased 4-6-fold.

Bilateral ligation of the common carotid arteries (series IV) quickly caused CBV to fall in the cerebral cortex (Fig. 2a). The greatest decrease in CBV (down to 56%) was observed 11-25 min after the beginning of cerebral ischemia. During 3 h of ischemia, CBV remained depressed. According to data in [1], hypoperfusion of the cortex and white matter of the rabbit brain during ischemia lasted 14 days. In our experiments, with an increase in the duration of ischemia a tendency was

noted for CBV to recover. However, after 3 h of ischemia CBV was still only 84%, i.e., less than initially. These results are in agreement with those obtained by other workers who studied the dynamics of CBV during cerebral ischemia [1, 12]. The decrease of CBV took place against the background of an increase of 15% in the total BP. The pressure in the sinus, reflecting the pressure in the vascular system of the brain, fell to 34.1 ± 2.7 mm Hg and remained at that level, 59% of the initial value. Immediately after the beginning of ischemia there was a short-term decrease of 11% in the respiration rate, with recovery after the 2nd minute of ischemia, and a further increase by 4-17% above the initial level. From the 15th minute of ischemia, a regular alternate rise and fall of the respiration rate was observed with fluctuations of between +35% and —25% of the initial value. According to our own data and reports in the literature [2], ligation of the carotid arteries induces a transient (1 min) and slight constriction of the mesenteric microvessels of the rat ($p > 0.05$) and considerable disturbances of the microcirculation: slowing of the blood flow and stasis in some vessels, increased pavementing of the leukocytes, diapedesis of erythrocytes into the tissue. With an increase in the duration of ischemia these phenomena increased in degree and became irreversible in character. LMV did not contract.

Prophylactic administration of LE (series V) was accompanied by an increase of 20% in CBF and the same changes in the hemodynamics and microcirculation as were observed in the experiments of series III. Immediately after ligation of the common carotid arteries the rise of CBV ceased, and it began to fall to its initial level, at which it remained throughout the rest of the experiment (Fig. 2b). After 2 h of ischemia CBV increased significantly (by 61%), but because of the wide scatter of the data between individual experiments these changes were not statistically significant ($p > 0.05$). Correlation was found between the primary response of CBV to LE and the subsequent changes in CBV during ischemia: the greater the increase in CBV during the first few minutes after administration of LE, the greater the likelihood of recovery and the greater the degree of increase of CBV during ischemia, and conversely, the smaller the increase in CBV in response to LE, the more frequent and greater the decrease and the slower the recovery and less marked the increase in CBV during ischemia. This relationship evidently reflects individual differences between the animals.

The therapeutic use of LE (series VI) significantly altered the trend of CBV during cerebral ischemia. Reduction of CBV after ligation of the vessels was stopped by injection of LE (Fig. 3). CBV regained its initial level 10 min after injection of LE. This was followed by a progressive increase in CBV with time, with a maximal increase of 54%. However, just as in series V, 2-3 h after the beginning of ischemia the increase in CBV compared with initially was no longer statistically significant ($p > 0.05$). The hemodynamics and microcirculation did not differ from those in series V: in the mesentery contractility of LMV was increased, but as in series III of the experiments disturbances of the microhemodynamics appeared later and were less marked than in series IV.

Thus irrespective of the time of its administration — before or after the beginning of ischemia — LE not only prevented any further decline of CBV during ischemia but also contributed to the rapid recovery of the initial value, with a tendency to increase further. Preservation of CBV in the cortex during moderately severe cerebral ischemia with the aid of LE may be due to the action of several factors. First, the direct influence of the opioid peptide on the opiate receptors of the brain and neurons of the vasomotor center in the medulla. However, in the control, when different ways of introducing LE into the brain were used (intracisternal, into the cerebral ventricles, by microiontophoresis , into the main vessels of the brain, and also by intraarterial and intravenous injection), according to data in the literature [7, 13] such a prolonged and considerable increase in CBV was not observed as we ourselves obtained as a result of intraperitoneal injection. The fact also is noteworthy that improvement of the hemodynamics and of the lymphatic circulation under the influence of LE is unconnected with intensification of cardiac activity, for bradycardia and lowering of BP are characteristic effects of LE on the heart. Vasodilatation of peripheral microvessels (in our experiments, mesenteric), plays a more important role, promoting reduction of the total peripheral resistance. This state of affairs is confirmed by experiments [13] which showed a decrease in the resistance of the vessels of the carotid and vertebrobasilar basins under the influence of LE, and also a decrease in cardiac output and the total peripheral resistance under the influence of the LE analog, dalargin [4]. By way of hypothesis, to explain the results described above, the improvement of CBV during ischemia under the influence of LE can be regarded as the result of optimization of the hemodynamics as a whole, linked with powerful stimulation of the micro- and macrolymphatic circulation by one of the most effective lymphatic stimulators. The increase in lymph formation and lymph drainage under the influence of opioid lymphatic stimulators may be an effective method of correcting disturbances of the lymphatic and blood circulation, not only in cerebral ischemia, but also in other pathological states accompanied by functional insufficiency of the heart, kidneys, lungs, etc.

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TRIGEMINAL NEURALGIA OF NEUROPATHIC ORIGIN

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In trigeminal neuralgia the onset of the disease is often associated with compression of a root [19] or of the II-III branches of the trigeminal nerve [3]. The development of gross destructive changes in the nerve is accompanied by a change of the disease into a neurotic stage, in which pain becomes continuous in character and is described by the patients as aching, stabbing, and burning.

To create models of trigeminal neuralgia, various neurochemical agents are widely used (tetanus toxin, penicillin, strychnine, picrotoxin), applied to the caudal trigeminal nucleus [6, 18]. These procedures lead to insufficiency of the mechanisms of inhibitory control and hyperactivation of neurons, and this is connected with the formation and activity of a generator of pathologically enhanced excitation (GPEE) [7]. Clinical physiological studies also have shown that the pathogenesis of trigeminal neuralgia is based on the formation of a GPEE in central structures of the trigeminal nerve system [5, 12].

Since the initial pathogenetic mechanism leading to the formation of a central GPEE in most cases is damage to peripheral portions of the trigeminal nerve system [5, 9], the aim of the investigation described below was to create models

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