Thus despite its short half-life, TRH can induce long-term changes in the BM balance in individual brain structures; this may be one explanation of the mechanism of the prolonged action of TRH in experimental pharmacology and clinical medicine.

LITERATURE CITED

1. V. J. Kluša, Peptides as Regulators of Brain Functions [in Russian], Riga (1984).
2. C. J. Early and B. E. Leonard, J. Pharm. Meth., 1, 67 (1978).
3. A. J. Kastin, R. H. Ehrensing, D. S. Schach, and M. S. Anderson, Lancet, 2, 740 (1972).
4. T. Mitsuma and T. Nogimori, Experientia, 39, 620 (1983).
5. A. J. Prange, I. C. Wilson, P. P. Lara, et al., Lancet, 2, 999 (1972).

AN OPIATE COMPONENT IN REALIZATION OF THE VASCULAR EFFECTS OF CLONIDINE

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Opiate receptors have been shown to participate in realization of the hypotensive action of clonidine in spontaneously hypertensive rats and in some patients with arterial hypertension. Analysis of naloxone-clonidine interaction in other investigations gave contradictory results. For example, naloxone inhibited the hypotensive and bradycardic effect of clonidine in normotensive rats and cats [1] and in man, whereas the results of other investigations showed that the cardiovascular effects of clonidine are realized without the participation of opiate receptors [14, 15].

In previous investigations clonidine-naloxone interaction was assessed purely on the basis of changes in blood pressure (BP) and heart rate (HR). Meanwhile the role of the cardiac and vascular components, which determine the response of BP, remained unknown.

The aim of this investigation was to study changes in the systemic and regional hemodynamics induced in anesthetized cats by clonidine and naloxone.

EXPERIMENTAL METHOD

Experiments were carried out on 18 cats of both sexes weighing from 2 to 5 kg. The animals were anesthetized with urethane and chloralose (430 ± 43 mg/kg, intramuscularly) and polyethylene catheters were introduced into the femoral artery and the femoral and external jugular veins. The cats were artificially ventilated and thoracotomy performed in the fourth left intercostal space. The transducer of a "Narcomatic RT-500" electromagnetic flow-meter was placed on the ascending part of the arch of the aorta and a catheter introduced into the left atrium. During the experiment the animals' body temperature was kept at 37 ± 0.5°C and the CO_2 concentration in the expired air at between 3.5 and 4.0 vol. %.

In the course of the experiment BP, HR, the pressure in the left atrium, the contractility (CV) of the left ventricle (dF/dt -- acceleration of the blood flow in the aorta), cardiac output, and blood flow in several organs and tissues were recorded with the use of microspheres (15 μ), labeled with ^{125}I, ^{141}Ce, ^{51}Cr, ^{85}Sr, and ^{46}Sc (from 3M Company, USA), by the method described previously [8].

All the substances for testing were dissolved in physiological saline and injected intravenously in the course of 10 min. Clonidine hydrochloride (from Boehringer, West Germany) was injected at the rate of 1 μg/kg/min, naloxone hydrochloride (from Endo Laboratories, USA) at the rate of 0.1 mg/kg/min.

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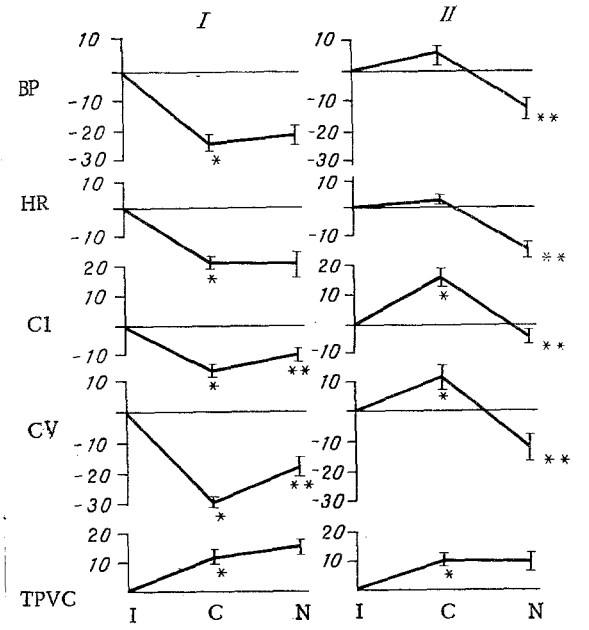

Fig. 1. Changes in parameters of systemic hemodynamics (in % of initial value) under the influence of consecutive injection of clonidine (10 μg/kg body weight) and naloxone (1 mg/kg) (experiments of series I) and after consecutive injection of naloxone and clonidine in the same doses (II). *P < 0.05 compared with initial value, **P < 0.05 compared with previous measurement. I) Initial level, C) clonidine, N) naloxone.

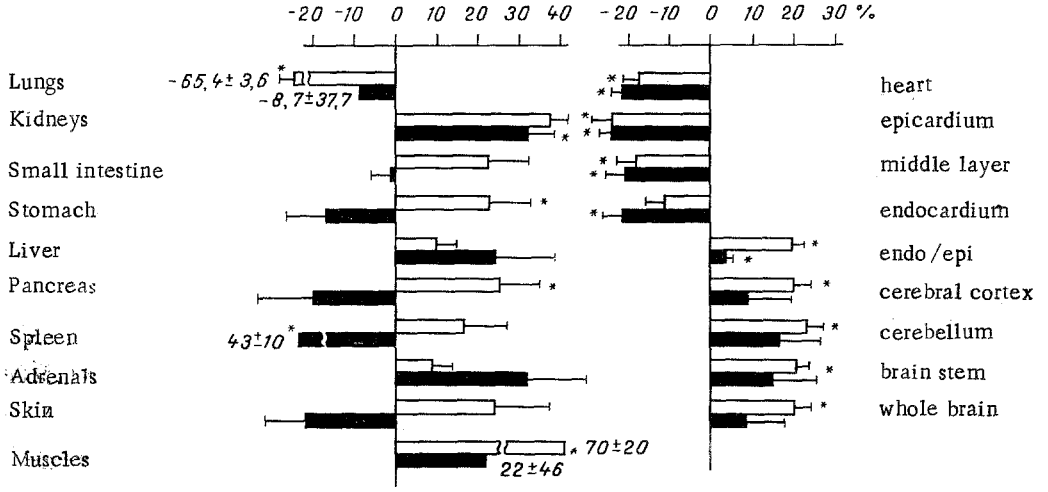

Fig. 2. Comparison of changes in regional vascular conduction under the influence of clonidine (unshaded columns, series I) and of clonidine preceded by naloxone (black columns, series II). *P < 0.05 compared with original value.

In the experiments of series I clonidine was injected first, and infusion of naloxone began immediately after the end of clonidine administration. The hemodynamic parameters were recorded before injection of clonidine (initial data), immediately after injection of the

total dose of clonidine (10 μg/kg), and after injection of the total dose of naloxone (1 mg/kg). In the experiments of series II naloxone was injected first, followed by clonidine. Otherwise the scheme was unchanged.

The significance of differences was estimated by Student's t test and the Mann–Whitney U test, using a package of standard programs for the PDP 11/34 computer.

EXPERIMENTAL RESULTS

Clonidine (Fig. 1), in a dose of 10 μg/kg (series I), caused BP to fall by 29.9 ± 3.6 mm Hg ($P < 0.05$), the heart rate (HR) to fall by 43.2 ± 4.6 beats/min ($P < 0.05$), the cardiac index (CI) to fall by 15.3 ± 2.4 ml/min/kg ($P < 0.05$), and CV to fall by 185 ± 30 ml/sec^2, but led to an increase in total peripheral vascular conduction (TPVC) by 0.09 ± 0.02 ml/min/kg/mm Hg ($P < 0.05$). Against the background of the action of clonidine the blood flow was significantly reduced in the lungs (arterial blood flow from the systemic circulation), liver, skin, adrenals, heart, and cerebral cortex, but at the same time it was increased in the skeletal muscles and kidneys (Fig. 2).

Naloxone, injected after clonidine, had no significant effect on BP (Fig. 1), HR, or TPVC, but increased CI by 5.00 ± 0.96 ml/min/kg and CV by 61.0 < 17.5 ml/sec^2. In most parts of the body naloxone did not affect the blood flow, except in the lungs (an increase of 12.7 ± 2.4 ml/min/100 g) and skin (a decrease of 0.33 ± 0.09 ml/min/100 g).

Thus according to the results of the experiments of series I no clear antagonism could be found between the effects of clonidine and naloxone.

In the experiments of series II naloxone was injected first (1 mg/kg), followed by clonidine. Naloxone did not affect the basic parameters of the systemic hemodynamics (BP, HR), but significantly increases CI by 18.1 ± 3.4 ml/min/kg and CV by 76.6 ± 21 ml/sec^2 (Fig. 1).

Naloxone significantly increased the coronary blood flow (by 45.2 ± 11.1 ml/min/100 g) and the blood flow in the cerebral cortex (by 2.7 ± 1.1 ml/min/100 g). In the remaining organs and tissues no significant changes were found in the blood flow.

Clonidine, injected after naloxone, caused a significant fall of BP by 28.1 ± 5.4 mm Hg, of HR by 40.2 ± 5.8 beats/min, and of CI by 25.7 ± 5.4 ml/min/kg, but there was no change whatever in TPVC (Fig. 1). Under the influence of clonidine the blood flow fell sharply in the abdominal organs (stomach, spleen, pancreas) and also in the skin and heart.

Comparison of the effects of clonidine in the experiments of series I and II (Fig. 2) shows modification of the vasodilator action of the drug in the abdominal organs into vasoconstrictor, if it was injected when opiate receptors were blocked.

The ability of clonidine to cause a fall of BP and HR is widely known. In the present experiments on anesthetized cats with an open chest, the causes of the fall of BP were a reduction in cardiac output by 15.1% and an increase in the total vascular conductivity by 11.3%. The increase in the total vascular conductivity was associated with dilatation of vessels of the abdominal organs, skeletal muscles, kidneys, and brain. Injection of naloxone when the effect of clonidine had already developed caused virtually no change in the basic parameters of the systemic and regional hemodynamics. Similar results were obtained in experiments on cats when BP and HR were recorded with the use of similar levels of anesthesia and similar doses of clonidine and naloxone [4].

Incidentally, when clonidine was injected into animals whose opiate receptors were blocked by naloxone, the character of the effects of clonidine was changed: The increase in total vascular conductivity disappeared and the vasodilatpr reaction in the abdominal vessels disappeared or were modified into constrictor. The absence of two-way antagonism between the cardiovascular effects of clonidine and naloxone also was found in an investigation of the baroreceptor reflex [13] and changes in BP and HR [4]. It can be tentatively suggested that for some of the vascular effects of clonidine (for example, vasodilatation in the abdominal organs) to develop, normally functioning opiate receptors are needed, whereas to maintain a response which has already developed, these receptors are not essential. Indirect confirmation of this hypothesis is given by the results of investigations in which peptide agonists of μ-opiate receptors induced significant changes in sensitivity of the baroreceptor reflex in man only after 3 h had elapsed, and this was attributed to the action of hypothetical secondary mediator [12]. The neurochemical basis for realization of opiate-dependent vasodilatation in the abdominal organs under the influence of clonidine may consist of enkephalins, which have been found in

the arterial wall of the abdominal organs in cats [10].

Previous investigations on animals and men showed that naloxone does not cause changes in BP or HR [3-5, 7, 12]. The results of the present experiments confirm that BP was unchanged after injection of naloxone, but they also showed that naloxone can stimulate the work of the heart: both CV and CI were increased. The mechanism of potentiation of cardiac function under the influence of naloxone is not clear. One possible explanation is based on the antinarcotic action of naloxone, its ability to block the opiate component in the action of general anesthetics [2]. In this case it can be postulated that partial blockage of the narcotic effect of the anesthetic was accompanied by potentiation of sympathetic influences predominantly on the heart, but not on the blood vessels. Demonstration of Leu- and Met-enkephalin in the mammalian heart [9] and the stimulating effect of naloxone on contraction of the isolated cat papillary muscle [5] suggests a peripheral mechanism in the action of naloxone.

The results of this investigation thus support the view that endogenous opioid substances have a tonic inhibitory influence on cardiac activity. It can be tentatively suggested that endogenous opioid substances play a triggering role in the development of vasodilator reactions in abdominal vessels induced by clonidine.

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LITERATURE CITED

1. A. V. Val'dman, O. S. Medvedev, and N. I. Rozhanskaya, Byull. Éksp. Biol. Med., No. 11, 560 (1981).
2. J. D. Arndt and E. Freye, Nature, 277, 399 (1979).
3. L. D. Byrd, Life Sci., 32, 391 (1983).
4. S. H. H. Chan, Exp. Neurol., 84, 338 (1984).
5. M. T. Curtis and A. M. Lefer, Am. J. Physiol., 239, H416 (1980).
6. C. Farsang, J. Kapocsi, I. Vaida, et al., Circulation, 69, 461 (1984).
7. C. Farsang and G. Kunos, Br. J. Pharmacol., 67, 161 (1979).
8. R. P. Hof, Basic Res. Cardiol., 75, 747 (1980).
9. R. E. Lang et al., Life Sci., 32, 399 (1983).
10. L. I. Larsson and K. Stengaard-Pedersen, J. Neurosci., 2, 861 (1982).
11. R. B. Resnick, A. M. Washton, and H. Lal, in: Endogenous and Exogenous Opiate Agonists and Antatonists, New York (1980), pp. 565-570.
12. P. C. Rubin, Clin. Sci., 66, 625 (1984).
13. H. L. Santiesteban et al., Fed. Proc., 41, Abst. No. 7280 (1982).
14. A. T. Shropshire and R. L. Wendt, J. Pharmacol. Exp. Ther., 224, 494 (1983).
15. J. Watkins et al., Clin. Pharmacol. Ther., 28, 605 (1980).