intact ones, but this difference virtually disappeared if the activity increase is assessed against the basal level. This reflects selective activation of NE release in response to the given stimulus by the sympathetic terminals, and not by the adrenal medullae.

REFERENCES

1. A. I. Kuz'min, V. S. Shul'zhenko, O. S. Medvedev, V. I. Kapel'-ko, *Byull. Vsesoyuz. Kardiol. Nauch. Tsentra*, No. 1, 75-82 (1987).
2. O. A. Tyurmina, L. A. Konlei, and O. S. Medvedev, *Eksp. Klin. Farmakol.*, **56**, No. 2, 21-24 (1993).
3. O. A. Tyurmina, A. I. Kuz'min, and O. S. Medvedev, in: *The Program "Russian Universities" (Medicine)* [in Russian], Moscow (1994), pp. 194-200.
4. R. J. Bialik, J. W. Smythe, M. Sardelis, and D. C. Roberts, *Brain Res.*, **502**, 88-98 (1989).
5. A. Deka Starosta, M. Garty, Z. Zukowska Grojec, *et al.*, *Am. J. Physiol.*, **257**, No. 1, Pt. 2, R229-R236 (1989).
6. M. Esler, G. Jennings, P. Korner, *et al.*, *Am. J. Physiol.*, **247**, No. 1, Pt. 1, E21-E28 (1984).
7. M. Garty, A. Deka Starosta, R. Stull, *et al.*, *Biol. Amines*, 7, No. 5, 435-444 (1990).
8. B. Hokfeld and S. Bydgeman, *Proc. Soc. Exp. Biol. Med.*, **106**, 537-542 (1961).
9. R. F. Kirby, M. F. Callahan, and A. K. Johnson, *J. Auton. Nerv. Syst.*, **20**, 185-188 (1987).
10. R. Kvetnansky, R. McCarty, C. R. Lake, and I. J. Kopin, *Am. J. Physiol.*, **236**, H457-H462 (1979).
11. O. S. Medvedev, M. Delle, and P. Thoren, *Clin. Exp. Hypertens. [A]*, **10**, Suppl. 1, 375-381 (1988).
12. O. S. Medvedev, A. I. Kuz'min, V. N. Selivanov, *et al.*, in: *Central Neural Mechanisms in Cardiovascular Regulation*, G. Kunos and J. Cirielo (Eds.), Boston (1991), pp. 244-253.
13. G. A. Smithe, H. S. Grunstein, J. E. Bradshow, *et al.*, *Nature*, **308**, 65-67 (1984).
14. C. L. Sun, N. B. Thoa, and I. J. Kopin, *Endocrinology*, **105**, 306-311 (1979).
15. J. Zabludowski, S. Clark, S. Ball, *et al.*, *Am. J. Physiol.*, **246**, H683-H689 (1984).

Nonopioid Nature of the Pressor Effect of FMRF-Amide

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The effect of the peptide FMRFa on arterial pressure, heart rate, and respiratory rate is examined in anesthetized rats. It is demonstrated that the effect of FMRFa is similar to that of epinephrine and is characterized by transient hypertension against the background of bradycardia and decreased respiratory rate followed by hypotensive phase. Opiate antagonists and agonists do not modify the effect of FMRFa. Pressor effect of FMRFa is inhibited by Aminazine and is abolished by dihydroergotamine, while clopheline, reserpine, propranolol, Dimedrol, and adrenalectomy have no appreciable effect on it. It is suggested that the effects of FMRFa are realized via vascular adrenoreceptors.

Key Words: *FMRFa; opioids; hypertension; adrenoreceptors*

The tetrapeptide Phe-Met-Arg-Phe-NH_2 (FMRFa) is a paraopioid [1] exhibiting pronounced therapeutic activity under conditions of clinical death and hypobaric hypoxia [2,7]. FMRFa produces hypertensive effects in intact rats [4,9]. The physiological mechanisms of these effects are obscure. In the present study we analyzed the possible mechanisms underlying cardiohemodynamic effects of FMRFa.

MATERIALS AND METHODS

Experiments were performed on 49 albino rats of both sexes (body weight 180-220 g) under Nembutal anesthesia. Before experiment, tracheotomy was per-

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formed and catheters were inserted into the common carotid artery for arterial pressure (AP) measurements and into the femoral vein for FMRFa infusions. To prevent blood coagulation the rats were injected with 500 U/kg heparin. The autonomic functions were assessed by measuring heart rate (HR), respiratory rate (RR) and mean AP, which were recorded by the standard methods throughout the entire experiment. FMRFa was infused intravenously in a dose of 0.1 mg/kg in 0.1 ml of normal saline.

Pharmacological analysis was carried out after administration of the peptide against the background of dihydroergotamine (1.0 mg/kg), Aminazine (25.0 mg/kg), clopheline (0.5 mg/kg), propranolol (1.0 mg/kg), atropine (5.0 mg/kg), Tremblex (0.1 mg/kg), Dimedrol (5.0 mg/kg), reserpine (5.0 mg/kg 24 h and 4 h before experiment), naloxone (5.0 mg/kg), fentanyl (0.005-0.01 mg/kg), and dalargin (0.25 mg/kg). All preparations were infused intravenously; clopheline and reserpine were injected intraperitoneally. In a separate series of experiments, FMRFa was injected against the background of adrenalectomy, vagotomy, and stabilized respiration. The cardiohemodynamic effects of FMRFa were compared with those of norepinephrine (0.1 mg/kg intravenously) and YGGFMRF-amide (0.1 mg/kg intravenously). Each rat received 1-3 infusions of FMRFa at 15-30-min intervals. The significance of differences was evaluated by standard Fischer's and Student's tests.

RESULTS

In the control series (n=12), FMRFa induced two-phase changes in AP, HR, and RR (Fig. 1). High transient (3-3.5 min) hypertension was observed immediately after infusion of FMRFa. By the 30th sec after infusion, AP increased by 50 mm Hg and then (4th min) dropped 29.4 mm Hg below the initial level. An increase in AP was accompanied by a decrease in HR (by 170 beats/min on average) and a decline in RR to apnea. Normalization of HR and respiration were observed as AP decreased; moderate tachycardia and tachypnea occurred during the hypotensive phase of FMRFa effects. All parameters reached the norm after 10-15 min. It was found that rats develop pulmonary edema within 1.5-2 h; some animals died 5-10 min after administration of FMRFa. These animals were excluded from statistical analysis.

When FMRFa was infused against the background of the opiate antagonist naloxone (n=7) and opiate agonists fentanyl (n=6) and dalargin (n=4), hemodynamic and respiratory parameters did not differ considerably from the control (Fig. 2), which argues against the antiopioid activity of the peptide [6,11]. It should be noted that the endogenous opioid

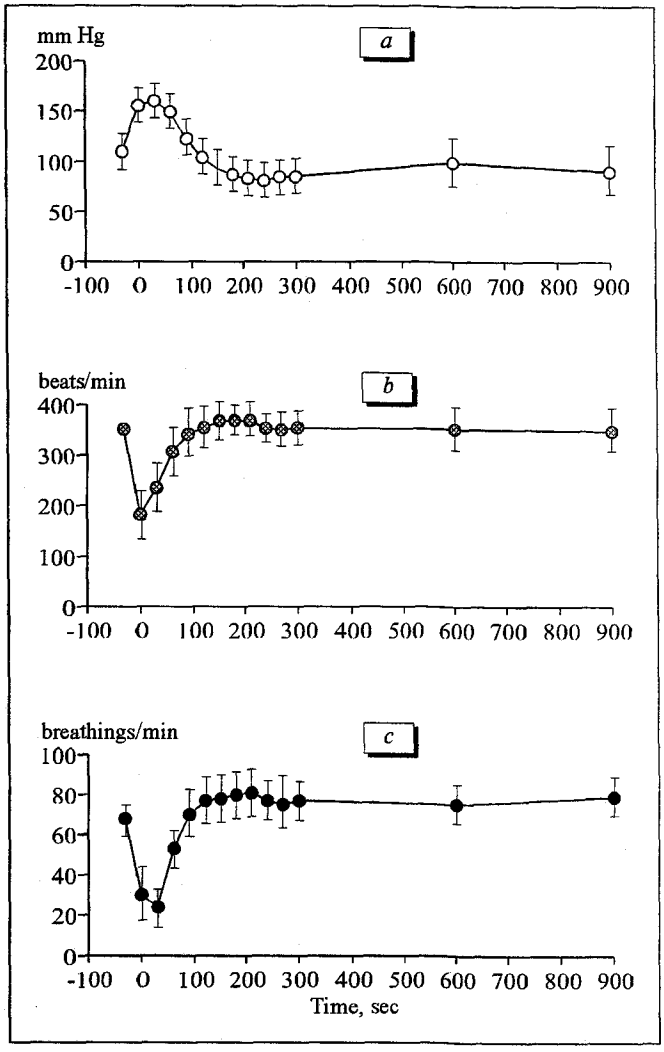

Fig. 1. Effect of FMRFa on arterial pressure (*a*), heart rate (*b*), and respiratory rate (*c*) in rats.

peptide YGGFMRFa, a tentative FMRFa precursor, induced a transient (30-60 sec) hypotension accompanied by moderate bradycardia (n=7); this effect was blocked by naloxone.

Vagotomy (n=3) and administration of atropine (n=6) abolished, while blockade of central cholinergic structures by Tremblex (n=6) inhibited FMRFa-induced bradycardia, producing no statistically significant effects on AP and RR. After administration of FMRFa to artificially ventilated rats (n=4), cardiohemodynamic parameters did not differ significantly from the control, although HR was significantly higher during the hypotensive phase. Dimedrol (n=5) and propranolol (n=6) abolished this effect and potentiated subsequent tachycardia.

Sympatheticoadrenal system is known to be involved in the realization of the effects of FMRFa [4]. However, in our experiments the central adrenolytic clopheline (n=9) as well as adrenalectomy (n=3) and

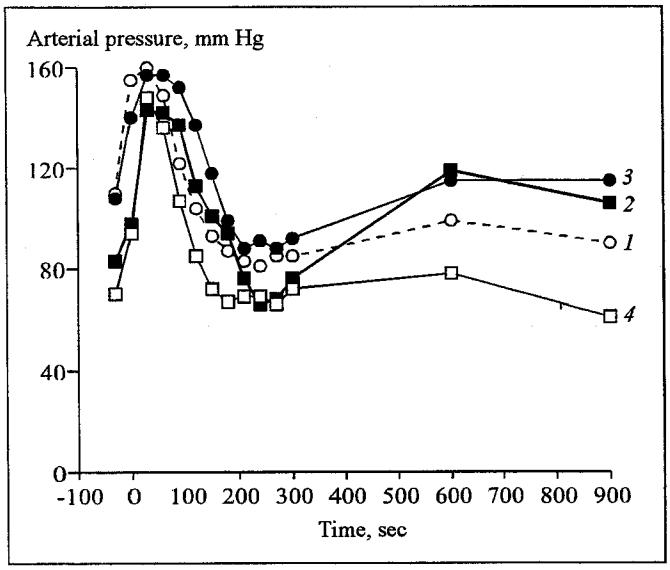

Fig. 2. Pressor effect of FMRFa (*1*) against the background of fentanyl (*2*), dalargin (*3*), and naloxone (*4*).

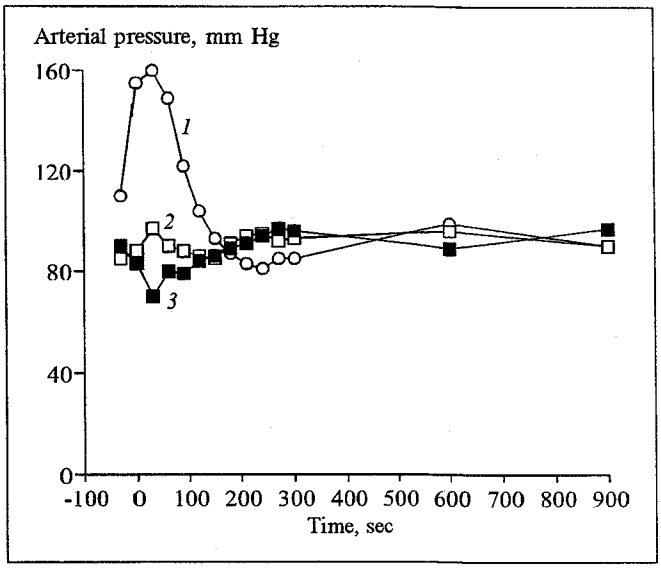

Fig. 3. Effects of Aminazine (*2*) and dihydroegrotamine (*3*) on pressor effect of FMRFa (*1*).

depletion of endogenous catecholamine stores with reserpine (n=5) produced no appreciable effects on respiratory and hemodynamic effects of FMRFa.

Against the background of the central and peripheral adrenoblocker Aminazine (n=6) the peptide produced a weak pressor effect attended by pronounced tachycardia (Fig. 3): AP increased by 12.2 mm Hg, HR increased by 59.4 beats/min, while RR remained unchanged. The peripheral adrenoblocker dihydroergotamine (n=6) abolished pressor effect of FMRFa, which was accompanied by pronounced tachycardia (Fig. 3). Arterial pressure decreased by 19.5 mm Hg, while HR increased by 85 beats/min. Respiratory rate did not change. It should be noted that norepinephrine (n=4) modified AP, HR, and RR similarly to FMRFa, although without the hypotensive phase and with significantly greater tachycardia.

Thus, we have shown that intravenous infusion of 0.1 mg/kg FMRFa induces a two-phase AP response in intact rats. This response coincides with modulations of respiratory and cardiac activities. Hypertensive activity of the peptide does not depend on activation or blockade of opiate receptors and is realized via adrenergic mechanisms. Presumably, the role of the central adrenergic mechanisms in the pressor effect of the peptide is minimal, and the effect is not associated with the release of endogenous catecholamines. Bearing in mind that epinephrine induces a two-phase hemodynamic response, which is similar to that observed in FMRFa-treated rats [3,5], and the fact that FMRFa inhibits anxiogenic effect of yohimbine and reduces insulin secretion by perfused pancreas [8,10], it can be suggested that cardiohemodynamic effects of systemically administered FMRFa result from direct activation of peripheral adrenergic receptors, i.e., it acts as an endogenous peptide ligand of these receptors.

REFERENCES

1. I. P. Ashmarin, *Itogi Nauki i Tekhniki. Ser. Fiziologiya Cheloveka i Zhivotnykh* [in Russian], Vol. 34, Moscow (1988), pp. 4-14.
2. I. Yu. Belov, T. V. Mamaeva, N. A. Sokolova, *et al.*, *Vestn. Mosk. Univer. Ser. Biologiya*, No. 4, 35-38 (1992).
3. E. N. Guseva, *Fiziol. Zh. SSSR*, **47**, No. 8, 958-964 (1961).
4. S. V. Zhukovskii, N. V. Korobov, V. I. Deigin, *et al.*, *Byull. Vsesoyuz. Kardiol. Nauch. Tsentra*, **12**, No. 1, 45-50 (1989).
5. O. A. Mikhaleva, *Fiziol. Zh. SSSR*, **47**, No. 7, 826-833 (1961).
6. N. A. Sokolova, Ya. V. Krushinskaya, V. B. Koshelev, *et al.*, *Usp. Fiziol. Nauk*, **25**, No. 4, 65 (1994).
7. R. L. Tinyakov, S. B. Parin, V. N. Krylov, *et al.*, *Byull. Eksp. Biol. Med.*, **121**, No. 4, 417-419 (1996).
8. H. C. Fehmann, G. McGregor, V. Weber, *et al.*, *Neuropeptides*, **17**, No. 2, 87-92 (1990).
9. G. Mues, I. Fuchs, E. T. Wei, *et al.*, *Life Sci.*, **31**, 2555-2561 (1982).
10. A. V. Muthal and C. T. Chopde, *Neuropeptides*, **27**, No. 2, 105-108 (1994).
11. J. Tang, H.-Y. Yang, and E. Costa, *Proc. Natl. Acad. Sci. USA*, **81**, No. 84, 5002-5005 (1984).