Shifts in Cardiac Indices Induced by Intravenous Leu-Enkephalin during Sympathetic and Parasympathetic Blockade in Rats

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Effects of intravenous leu-enkephalin on heart rate, stroke volume, and minute blood volume under conditions of sympathetic and parasympathetic blockade were studied in experiments on pubertal rats anesthetized with urethane. This opioid peptide inhibits sympathetic and parasympathetic control on the heart, affecting not only chronotropic but inotropic cardiac indices.

Key Words: *leu-enkephalin; impedance cardiogram; sympathetic blockade; parasympathetic blockade*

Opioid peptides produce considerable effects on cardiovascular system, particularly in stress [1]. Their action is associated with autonomic nervous system. It was shown that opioid peptides (enkephalins) inhibit adrenergic control on the myocardium. They suppress the release of endogenous catecholamines, peripheral effects of adrenalin, and cAMP rise [2,3, 5]. Inhibitory effect of enkephalins on the parasympathetic system, including its chronotropic influence, has been confirmed [4]. Thus, opioid peptides suppress neurotransmitter release both in cholinergic and adrenergic synapses [7,9]. However, the inhibition of extracardial regulation by leu-enkephalin was considered mainly in view of its chronotropic effect: is little known about its inotropic effect.

We studied the effect of leu-enkephalin on sympathetic and parasympathetic control of the heart. Heart rate (HR), stroke volume (SV), and minute blood volume (MBV) were measured.

MATERIALS AND METHODS

Experiments were carried out on 80 albino rats weighing 130-160 g. The animals were narcotized with intraperitoneal urethane (20%, 1.3 g/kg). HR, SV, and MBV values were obtained from the impedance cardiogram recorded with an RPG-4 electrocardiograph. Needle electrodes were fixed subcutaneously. Stimulating electrodes were placed on the head and on the hind limb. Recording electrodes were located along the collar bones in the front of the thorax and at the arc between axila middle lines in the back side. Electrodes were arranged in the horizontal surface crossing the lower margin of the sternum. The cardiac performance parameters were recorded before and after leu-enkephalin (Vektor, Kol'tsovo, Novosibirsk region) administration for 10 min; the records consisted of 5-sec fragments at the end of each minute. In the first series, leu-enkephalin (56.7 mg/kg) was injected in the left jugular vein. In the second series, it was infusion after sympathetic blokade by benzohexonium (100 mg/ml) or Obzidan (0.8 mg/kg). In the third series, leu-enkephalin was infused after parasympathetic blokade by atropine (0.3 mg/100 g). The results were statistically analyzed by standard ANOVA methods with a significance level of $p<0.05$ for Stu-dent's t test.

RESULTS

Immediately after leu-enkephalin infusion HR decreased from 420.8±3.42 (initial value) to 412.35±4.2

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beats/sec, reached the minimum (408.24±4.86 beats/sec, 3% reduction; $p<0.05$) after 2 min, then gradually increased, and returned to the initial level at the end of the 5th min. Two minutes after the infusion, SV decreased from 0.272±0.02 ml to 0.235±0.02 ml (by 13.61 %), and MBV from 114.16±11.2 to 96.73±9.83 ml/min (by 15.27 %). Thus, leu-enkephalin produced not only chronotropic but also inotropic inhibitory effects on cardiac function.

Administration of benzohexonium significantly decreased all cardiac indices. After benzohexonium, leu-enkephalin on the first minute postinjection raised HR by 2.04% (from 348.5±8.7 to 356±6.8 beats/sec, $p>0.05$, Fig. 1). The pronounced growth of SV (from 0.039±0.002 ml to 0.070±0.002 ml, 36.91%, $p<0.05$%) and MBV (from 13,59±2.85 ml/min to 24.9±2.0 ml/min, 34.98%, $p<0.05$%) occurred on the 2nd min postinjection. The effect of leu-enkephalin on HR may be attributed to its inhibitory action on acetylcholine release in the cardiac parasympathetic ganglion [6,8].

Injection of Obzidan lowered HR and had practically no effect on SV and MBV. After Obzidan, leu-enkephalin slightly raised HR, SV, and MBV, the SV increase being statistically significant. The effect of leu-enkephalin was more pronounced after Obzidan-induced sympathetic blockade than after parasympathetic blockade by benzohexonium. This may be due to the fact that Obzidan selectively inhibits β-receptors, while α-receptors remain functionally active. On the one hand, leu-enkephalin suppresses the release of acetylcholine. On the other hand, it inhibits the release of adrenalin from sympathetic fibers. As a result, HR and MBV changed slightly (Fig. 2).

Atropine raised HR, SV, and MBV. Leu-enkephalin suppressed cardiac function in atropinized rats (Fig. 3). The maximum inhibitory effect was observed on the 2nd min after injection: SV decreased from

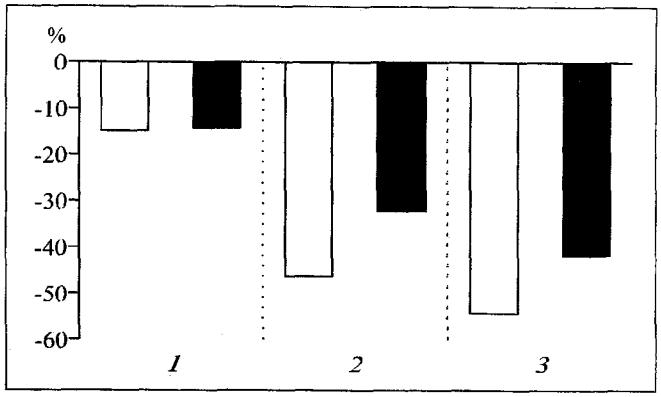

Fig. 1. Shifts in heart rate (*1*), stroke volume (*2*), and minute blood volume (*3*) after benzohexonium-induced blokade (white bars) and leu-enkephalin injection (black bars).

0.200±0.012 ml to 0.16±0.01 ml (21.39%), MBV from 76.86±4.30 ml/min to 59.12±4.05 ml/min (27.1%), HR decreased insignificantly. So, in conditions of enhanced cardiac performance under atropine-induced parasympathetic blokade leu-enkephalin lowered cardiac indices, particularly SV and MBV. It is likely that leu-enkephalin decreases acetylcholine release in the stellar ganglion and norepinephrine release from postganglionic nerve fibers. Inhibitory effect of leu-enkephalin on the release of sympathetic transmitter, which leads to HR reduction, has been demonstrated. Confirming these data, our results also demonstrate an inhibitory effect of leu-enkephalin on SV and MBV (Fig. 3).

Thus, intravenous leu-enkephalin reduces HR, SV, and MBV in the rat. Cardiac function depression can be explained by lesser amounts of neurotransmitters released in sympathetic and parasympathetic ganglia.

When sympathetic and parasympathetic systems are blocked, leu-enkephalin produces chronotropic and inotropic effects on the heart by restoring cardiac indices to the initial level. Leu-enkephalin increases

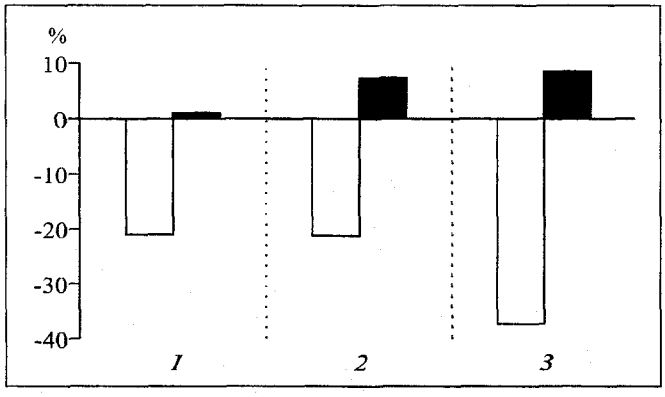

Fig. 2. Shifts in heart rate (*1*), stroke volume (*2*), and minute blood volume (*3*) after Obzidan-induced blokade (white bars) and leu-enkephalin injection (black bars).

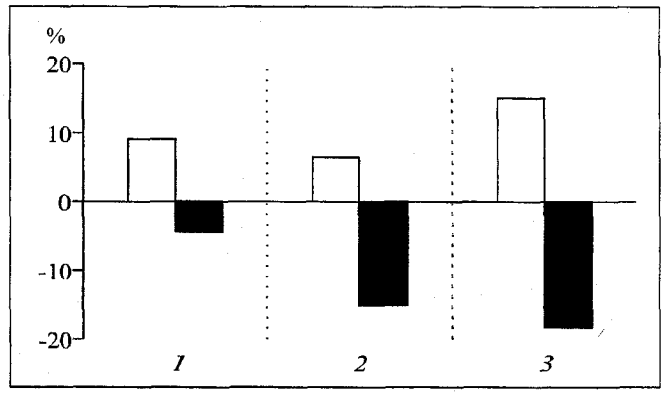

Fig. 3. Shifts in heart rate (*1*), stroke volume (*2*), and minute blood volume (*3*) after atropine-induced blokade (white bars) and leu-enkephalin injection (black bars).

HR, SV, while MBV decreased after sympathetic blokade caused by Obzidan and benzohexonium. This peptide inhibits chronotropic and inotropic effects of atropine on the heart.

REFERENCES

1. E. O. Bragin, In: *Neurochemical Mechanisms of Pain Sensation Regulation* [in Russian], Moscow (1991).
2. G. K. Zoloev, *Fiziol. Zhurn. SSSR*, **71**, No. 10, 1214-1216 (1985).
3. G. R. Ivanitskii, F. F. Beloyartsev, M. E. Sakson *et al.*, *Dokl. AN SSSR*, **261**, No. 3, 753-755 (1981).
4. V. M. Pokrovskii, Yu. R. Sheikh-Zade, *Fiziol. Zhurn. SSSR*, **68**, No. 8, 1112-1115 (1982).
5. W. Klce, A. Lampert, M. Nirenberg, In: *Opiates and Endogenous Opioid Peptides, 153-168, Escwier* (1976).
6. S. Konishi, A. Tsunoo, *Biomed. Res.*, No. 1, 528-536. (1980).
7. J. M. Lundberg, T.Hokfelt, *Trends Neurosci.*, N 8, 325-333 (1983).
8. J. M. Lundberg, T.Hokfelt, *Acta Physiol. Scand.*, **104**, 499-501 (1978)
9. Takashi Musha, Eisakee Saton, *J. Pharmacol. Exp. Ther.*, **250**, No. 3, 1087-1091 (1989).