Effects of β-endorphin on the contraction and electrical activity of the isolated perfused rat heart

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β-Endorphin at pharmacological doses reduced both the left ventricular systolic and diastolic pressures of the isolated rat heart. The reduction in the diastolic ventricular pressure was dose dependent. β-Endorphin also altered the electrical activities of the isolated heart, disturbing the normal electrocardiogram pattern. The degree of disturbance was also dose dependent. Naloxone itself did not produce any effect. However it antagonized the depressant effects and completely abolished the effect of β-endorphin on the electrical activity of the heart, indicating that β-endorphin acts via the naloxone sensitive receptors. The results suggest a possible regulatory role of intracardiac endogenous opioid peptides in the cardiac functions.

Key words: electrocardiogram; β-endorphin; isolated heart; left ventricular diastolic pressure; left ventricular systolic pressure; naloxone

It has been shown that morphine decreases the myocardial contractility and heart rate in an isolated heart preparation (1). These effects of morphine have been shown to be noncholinergic and nonadrenergic (2). Recently it has been demonstrated that opiate receptors are present in the heart (3), suggesting that endogenous opioid peptides may act directly on the heart. Since β-endorphin is secreted from the pituitary gland and is believed to act as a hormone, we studied the effects on β-endorphin on the contractility and electrical activity of the heart, using an isolated perfused rat heart preparation as described by Karmazyn *et al.* (4).

Female Sprague-Dawley rats (210–230 g) were employed. The rats were killed by decapitation. The heart was then rapidly excised and put into ice-chilled Kreb's ringer. The aorta was identified and the heart was then connected to a perfusion apparatus by aortic cannulation. All hearts were perfused retrogradely according to Langendorff technique at a constant flow rate of 3 ml/min at 70 mmHg perfusate pressure with oxygenated Kreb's ringer (pH = 7.4) containing (in nmol L^{-1}) NaCl 118, KCl 4.7, $MgSO_4$ 1.2, KH_2PO_4 1.1, $NaHCO_3$ 24, $CaCl_2$ 2.5 and glucose 10, warmed by a water bath at a constant temperature of 37° and equilibrated with 95% O_2:5% CO_2 mixture throughout the experiment. A water jacket was also provided for the entire system, maintaining the whole isolated perfused heart at 37°. A microsyringe (Hamilton) was positioned via the aortic cannula for the injection of drugs. Human β-endorphin from Peninsula Lab. and naloxone from Endo. Lab. were dissolved in the Kreb's ringer and

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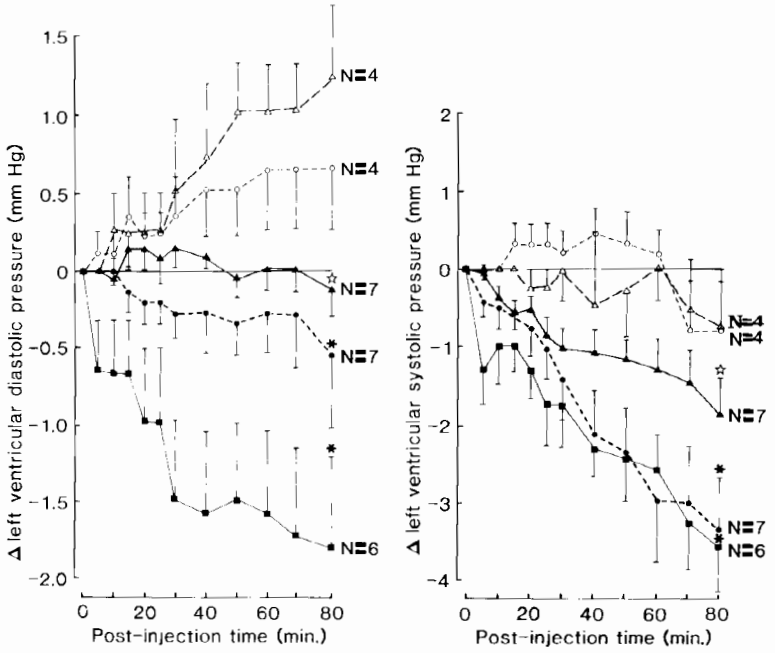

FIGURE 1

Changes in left ventricular pressures in the isolated heart following administration of β-endorphin. ○, Control. △, Naloxone 50 μg. ▲, β-endorphin 4 nmol, and pretreated with naloxone 50 μg. ●, β-endorphin 4 nmol. ■, β-endorphin 20 nmol.

The values are Mean + SEM. The pre-injection levels of the left ventricular diastolic pressures for the control group, groups receiving naloxone (50 μg), β-endorphin at the doses 4 nmol and 20 nmol, and the group receiving β-endorphin at the dose 4 nmol with naloxone (50 μg) pretreatment were 17 ± 2.46 mmHg (n = 4), 13 ± 0.48 mmHg (n = 7), 15 ± 1.21 mmHg (n = 7), 15 ± 0.69 mmHg (n = 6) and 13 ± 1.22 mmHg (n = 7), respectively. Those of the left ventricular systolic pressures for the same groups were 30 ± 2.56 mmHg (n = 4), 31 ± 1.29 mmHg (n = 4), 31 ± 2.81 mmHg (n = 7), 32 ± 3.52 mmHg (n = 6) and 33 ± 2.57 mmHg (n = 7), respectively. * and ☆ signify difference from the control group and the group receiving 4 nmol β-endorphin to the level $P < 0.01$ by unweighted means analysis of variance (5).

injected via the microsyringe. Naloxone was administered to the heart 10 min before injection of β-endorphin into the heart. The time of injection was 1 min. Intraventricular systolic and diastolic pressures were measured by inserting a 24-gauge needle through the apex of the heart into the left ventricle. The left ventricular pressures were then recorded on a polygraph by a Gould 2200S recorder via a pressure transducer (Statham). Electrocardiograms were monitored by a Heart Monitor System Model No. 633 BM (Fukuda, Japan) continuously, with a positive electrode hooked at the apex of the heart, a negative electrode at the atrium and a ground electrode at the pericardial tissues. The hearts were then allowed to equilibrate for 20–30 min before the experiment started. Any hearts showing functional instability during this period were discarded. Results were presented as time-course changes in pressures after injection. Unweighted mean analysis of variance was used to test differences between groups (5).

Fig. 1 presents the results of experiments on the effects of administration of β-endorphin on the left ventricular systolic and diastolic pressures in the isolated perfused heart. β-endorphin at doses 4 and 20 nmol decreased both ventricular systolic and diastolic pressures. The reduction in ventricular diastolic pressure was dose-dependent. The effects of β-endorphin were significantly attenuated with pretreatment

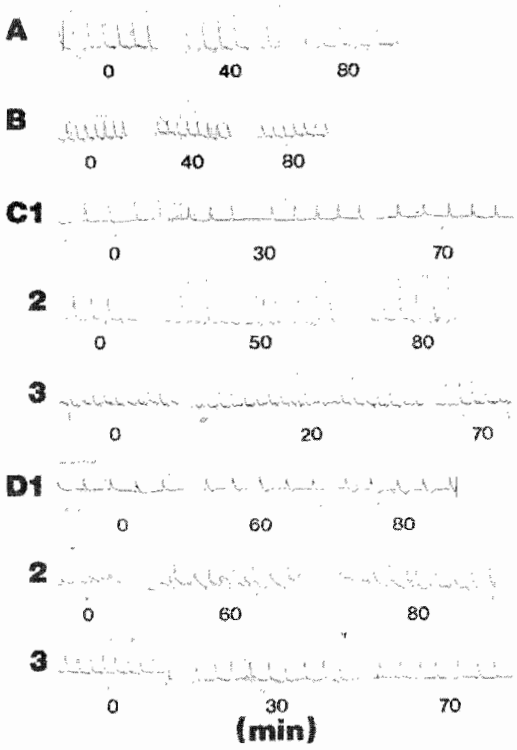

FIGURE 2

Changes in electrical activities in the isolated rat heart following administration of β-endorphin. A. Effects of administration of isotonic saline. There is no significant change. B. Effects of administration of 14 μg β-endorphin 10 min after pretreatment of 50 μg naloxone. There is no significant change. C. Effects of administration of 14 μg β-endorphin. Tracing 1 – irregular sinus rhythm with AV heart block at beat 4 after 30 min and recovery after 70 min. Tracing 2 – irregular sinus rhythm with paroxysmal atrial tachycardia at beats 1–7 and atrial premature beats at beats 9–12 after 50 min, and recovery after 80 min. Tracing 3 – irregular sinus rhythm with paroxysmal atrial tachycardia at beats 9–12 after 20 min and recovery after 70 min. D. Effects of administration of 69 μg β-endorphin. Tracing 1 – regular sinus rhythm with ST depression after 60 and 80 min. Tracing 2 – irregular sinus rhythm with atrial premature beats at beat 6 after 60 min, and at beat 6 after 80 min. Tracing 3 – irregular sinus rhythm with atrial fibrillation after 30 min and recovery after 80 min.

of naloxone 50 μg, which itself had no depressant effect on the isolated heart (Fig. 1). In addition β-endorphin at doses 4 and 20 nmol invariably caused cardiac arrhythmias as shown in Fig. 2. Of seven hearts that received 4 nmol of β-endorphin, one showed AV heart block, three atrial premature beats, two paroxysmal atrial tachycardia and one both atrial premature beat and paroxysmal atrial tachycardia (Fig. 2C). Injection of 20 nmol β-endorphin resulted in ST depression in two hearts, atrial premature beats in three hearts and atrial fibrillation in one heart (Fig. 2D). The results show that a higher dose of β-endorphin administered resulted in more pronounced changes in electrical activity of the heart. Naloxone at the dose 50 μg did not itself cause significant changes in the electrical activity but abolished completely the effects of β-endorphin.

The results in this study indicate that there is a direct effect of β-endorphin on the isolated perfused heart and this effect is via the naloxone sensitive receptors. The results are compatible with the depressant effects of morphine on the isolated rat heart (1) and of β-endorphin on the isolated pig papillary muscles (6).

In this study β-endorphin at doses 4 and 20 nmol was administered into the isolated heart in 1 min with a flow rate of 3 ml/min. The concentrations of β-endorphin are calculated to be 1.33 and 6.67 nmol/ml respectively, more than 1000 times higher than the physiological level of the immunoreactive β-endorphin in the blood of rats (7). The results do not support a physiological role of the circulating β-endorphin from the pituitary in the regulation of cardiac function.

Using immunohistochemical techniques Weihe *et al.* (8) were able to demonstrate the presence of a small amount of Met-enkephalin in the nerve fibres and some small cells (paraganglionic and APUD cells) of the heart, suggesting a possibility of Met-enkephalin being a neurotransmitter in the heart. In the present study β-endorphin administered to the isolated heart may reach the opiate receptors by non-specific diffusion and mimic an intracardiac neurotransmitter, which is likely to be Met-enkephalin. The pharmacological effects of β-endorphin as demonstrated in this study support the suggestion of a regulatory role

of intercardiac endogenous opioid peptide in the cardiac functions.

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