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NALOXONE INHIBITS EARLY ARRHYTHMIAS RESULTING FROM ACUTE CORONARY LIGATION

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The intravenous administration of naloxone 15 min before acute coronary artery ligation in both anaesthetized and conscious male rats markedly reduced the incidence and severity of the ventricular arrhythmias that occur within 30 min of the onset of myocardial ischaemia. The incidence of ventricular fibrillation was especially reduced and, in conscious rats, the survival 16 h after ligation was increased from 27% (in the controls) to 58 and 73% after 2 and 4 mg/kg naloxone respectively. One possible explanation of these results implies a detrimental effect of released endorphin in the early stages of myocardial ischaemia.

Introduction There is good evidence that β-endorphin is released from the pituitary gland during stress (Rossier, French, Rivier, Ling, Guillemin & Bloom, 1978) and this led Holaday & Faden in 1976 to consider the possibility that it is also released in circulatory shock states. They demonstrated that the opiate antagonist naloxone reverses the hypotension that results from bacterial endotoxaemia (Holaday & Faden, 1978), haemorrhage (Faden & Holaday, 1979) and spinal shock (Holaday & Faden, 1980) and also increases survival. These results have since been confirmed by others (reviewed by Parratt, 1982). We have now examined whether naloxone modifies the effects of another form of stress, namely, the ventricular arrhythmias and sudden cardiac death which result from acute coronary artery occlusion in conscious and anaesthetized male rats.

Methods The experiments were performed on male Sprague-Dawley rats weighing between 200 and 350 g. Two separate studies were carried out. In the first, rats were anaesthetized with pentobarbitone sodium (6 mg/100 g i.p.) and catheters were placed in a carotid artery (for pressure measurement) and in a femoral vein (for drug or vehicle administration). The electrocardiogram was recorded from standard limb leads. The rats were subjected to coronary artery ligation as previously described in detail, (Clark, Foreman, Kane, McDonald & Parratt, 1980) and the early postligation arrhythmias assessed by counting the number of ventricular ectopic beats during the initial 30 min postligation period and by measuring the incidence and duration of both ventricular tachycardia (VT) and ventricular fibrillation (VF) as previously described (Clark *et al.*, 1980). Naloxone (generously donated by Endo Laboratories) was given intravenously in a dose of 2 mg/kg followed by a continuous infusion of $1\,\mu g\,kg^{-1}\,min^{-1}$.

Because anaesthesia is known to inhibit the release of β-endorphin, a second study was performed in conscious rats using the method recently described in detail (Leprán, Siegmund & Szekeres, 1979; Kane, Leprán, McDonald, Parratt & Szekeres, 1980). In a preliminary operation under ether anaesthesia, a loose atraumatic silk loop was placed around the left coronary artery and a week later coronary occlusion was produced by tightening this loop. The electrocardiogram was recorded in these animals from electrodes implanted (under light ether anaesthesia) on both sides of the chest. Either naloxone (2 or 4 mg/kg) or saline (control group) was injected into a tail vein 15–20 min before coronary artery ligation and the severity of the arrhythmias occuring within 20 min of occlusion was assessed as previously described (Leprán *et al.*, 1979; Kane *et al.*, 1980; Leprán, Koltai & Szekeres, 1981). In those animals that survived 16 h the size of the infarcted area was assessed after staining with nitrobluetetrazolium (Clark *et al.*, 1980).

Results *Effect of naloxone on early post-ligation arrhythmias in anaesthetized rats* In the dose used naloxone had no effect on arterial blood pressure (systolic 116 ± 9 mmHg, diastolic 92 ± 7 mmHg before drug administration and 115 ± 8 mmHg and 89 ± 7 mmHg respectively 15 min after administration, when the coronary artery was ligated) or on heart rate (454 ± 9 to 453 ± 9 beats/min). Naloxone reduced the incidence of ventricular ectopic beats (VEBs) in the initial 30 min postligation period from 1486 ± 171 to 454 ± 82 ($P < 0.05$). This reduction was especially pronounced in the 11–25 min period (phase 1b arrhythmias) when there was a reduction from 712 ± 35 ectopic beats in the controls to only 117 ± 24 VEBs in the naloxone-treated group. The duration of VT during the initial 30 min postligation period was reduced from 65 ± 9 to 22 ± 9 s and the incidence and duration of VF was reduced from 50% and 27 ± 7 s to 10% and 6 ± 2 s ($P < 0.05$).

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Effect of naloxone on early postligation arrhythmias in conscious rats The results obtained in the conscious rats subjected to acute coronary artery occlusion are summarised in Table 1. They demonstrate firstly that survival in conscious rats subjected to acute coronary ligation is markedly increased by pretreatment with naloxone. For example, 73% of rats given the higher dose (2 mg/kg) were alive and well 16 h after coronary artery occlusion compared to only 27% of the control group ($P<0.01$). The reason for this increased survival was clearly the protection afforded by naloxone against the early, life-threatening arrhythmias (especially ventricular fibrillation) that occur within minutes of acute myocardial ischaemia. Thus the incidence (Table 1) of VF was significantly suppressed by naloxone as was the duration of VF when it occurred (e.g. from 12.5 ± 5.9 s in the controls and 5.0 ± 0.4 s in rats treated with 2 mg/kg naloxone). The appearance of ventricular arrhythmias after ligation was also delayed by naloxone (from 4.8 ± 0.2 s in the controls to 9.5 ± 1.7 s ($P<0.05$) and 11.0 ± 1.4 s ($P<0.001$) in rats treated with 2 and 4 mg/kg respectively). Although the incidence and severity of ventricular arrhythmias (other than VF) was also decreased (as in the experiments with anaesthetized rats) this reduction was neither significant nor as marked as the reduction in VF. For example, the duration of VT was reduced from 36.2 ± 5.0 s to 16.2 ± 8.6 and 18.8 ± 14.0 s (NS) in the rats given 2 and 4 mg/kg naloxone respectively. Naloxone did not significantly modify the increase in heart rate that occurs within the first few minutes of coronary artery ligation in this model (e.g. from 356 ± 9 beats/min preligation to 401 ± 15 beats/min postligation; $P<0.05$, in the control group) nor did it reduce the ultimate area of infarction which was 24 ± 3% of the ventricles in the control group and 22 ± 3% and 32 ± 4% respectively in those rats treated with 2 or 4 mg/kg naloxone.

Discussion A number of studies have demonstrated the effectiveness of naloxone in a variety of low tissue perfusion states. Soon after acute coronary artery ligation there is a marked, although regionally variable, reduction in blood flow and ventricular arrhythmias develop as an early consequence of this myocardial ischaemia. The present results illustrate clearly that naloxone in doses similar to those used in the shock studies, reduces both the incidence and severity of these early arrhythmias, and especially ventricular fibrillation. Indeed, 25–36% of the conscious rats had no post-ischaemia arrhythmias at all (Table 1). This antiarrhythmic effect is almost certainly responsible for the dramatic increase in survival in conscious rats subjected to coronary artery ligation (Table 1). These results taken together with those studies indicating the effectiveness of naloxone in various circulatory shock states could be interpreted as indicating that β-endorphin, perhaps released as a consequence of the stress of acute myocardial ischaemia, may have detrimental electrophysiological effects on the myocardium either directly (on myocardial opiate binding sites) or indirectly through central inhibition or activation of the autonomic nervous system. The fact that meptazinol, which has partial agonist activity at some opiate receptors, also affords similar protection early in myocardial ischaemia (Fagbemi, Kane, Leprán, Parratt & Szekeres, unpublished observations) is also suggestive that opiate receptors are involved in this protective action of naloxone. However, another possibility, for which there is at present no evidence, is that naloxone has direct effects on the cardiac muscle action potential.

Table 1 Effect of naloxone on the survival rate and occurrence of arrhythmias in the acute phase of experimental myocardial infarction in conscious rats

	n	*Survival after*				*Occurrence of arrhythmias*							
		20 min		*16 h*		*None*		*VF*		*VT*		*Other†*	
		n	%	n	%	n	%	n	%	n	%	n	%
Control	26	8	31	7	27	0	0	23	88	24	92	17	65
Naloxone													
2 mg/kg	12	8	67*	7	58	3	25**	7	58*	7	58*	4	33
4 mg/kg	11	9	82**	8	73**	4	36**	2	18***	3	27***	5	45

† Including single ventricular ectopic beats, atrioventricular block.
*$P<0.05$; **$P<0.01$; ***$P<0.001$ (Chi-squared test).

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