

Antiarrhythmic actions of meptazinol, a partial agonist at opiate receptors, in acute myocardial ischaemia

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1 The intravenous administration, to anaesthetized rats, of meptazinol (1 and 2 mg kg⁻¹), a partial agonist at opiate receptors, greatly reduced the incidence of ventricular extrasystoles that resulted from acute coronary artery occlusion. The incidence of ventricular fibrillation (VF) was reduced from 50% (in the controls) to 10% and the mortality from 30% to zero.

2 In similar doses, pretreatment with meptazinol also reduced ventricular arrhythmias, including fibrillation, in conscious rats subjected to coronary artery occlusion. In this model, survival at 16 h was increased from 27% in the controls to 50% and 83% respectively in rats pretreated with 1 and 2 mg kg⁻¹ of the drug.

3 In antiarrhythmic doses, meptazinol had little effect on either heart rate or systemic arterial blood pressure.

4 Intracellular action potential recordings from papillary muscle removed from rats given meptazinol (2 mg kg⁻¹) 15 min previously showed an increase in APD₅₀ and APD₉₀ of more than 40%. There was no effect on dV/dt_{max}. When superfused with meptazinol *in vitro* normal rat papillary muscle stimulated at 1 or 3 Hz showed an increase in APD₉₀ and a decrease in dV/dt_{max}.

5 The antiarrhythmic effect of meptazinol in these models can probably be explained by direct actions on the cardiac muscle action potential (increase in APD) although effects on opiate receptors cannot be ruled out. It is suggested that meptazinol might be useful in relieving pain, and in reducing the severity of arrhythmias in the early stages of acute myocardial infarction.

Introduction

Recent studies by the present authors, in both conscious and anaesthetized rats, have demonstrated that naloxone markedly reduces the incidence and duration of the serious ventricular arrhythmias that result from coronary artery occlusion. Survival, assessed 16 h after the onset of ischaemia, is also significantly increased (Fagbemi, Leprán, Parratt & Szekeres, 1982). There are two possible explanations for this protection; either the stress associated with the early stages of acute myocardial infarction leads to the release of an endogenous opiate (e.g. β -endorphin) which might have detrimental effects on cardiac function, or naloxone might possess directly mediated antiarrhythmic effects on the cardiac muscle action potential. As far as we are aware there is at present no evidence that this is so; in contrast, there is ample evidence for a protective effect of naloxone in

other shock states (endotoxaemia, haemorrhage, spinal shock; for references see Fagbemi *et al.*, 1982).

Meptazinol is a centrally acting analgesic which binds to opiate receptors (Stephens, Waterfall & Franklin, 1978) and is said to cause less respiratory depression and constipation than other opioid analgesics such as morphine and pentazocine (Stephens *et al.*, 1978; Jordan, Lehane, Robson & Jones, 1979). Like naloxone, meptazinol affords protection against shock induced by haemorrhage, endotoxin and anaphylaxis (Chance, Todd & Waterfall, 1981; Paciorek & Todd, 1982a, b) and the present studies were designed to explore the possibility that this partial agonist at opiate receptors might, like naloxone, also reduce the severity of the early, life-threatening arrhythmias that result from acute myocardial ischaemia.

Methods

Anaesthetized rats

Male Sprague-Dawley rats (250–350 g body weight) were anaesthetized with pentobarbitone sodium (60 mg/kg, i.p.) and artificially ventilated (stroke volume, 2 ml/100 g; 54 strokes/min). Carotid arterial blood pressure and a standard lead I or II electrocardiogram (ECG) were recorded using a mingograph 81 ink-jet recorder (Elema Schönander). A femoral vein was cannulated for drug administration. Rectal temperature was maintained at approximately 38°C. The chest was opened between the fourth and fifth ribs, approximately 2 mm to the left of the sternum. After opening the pericardium, the heart was exteriorized and a 6/0 silk suture was placed under the left coronary artery as described by Selye, Bajusz, Grasso & Mendell (1960). The heart was repositioned in the thoracic cavity, and the blood pressure and ECG allowed to stabilize for 15 min. Meptazinol, 1 or 2 mg kg⁻¹, or saline was administered intravenously 15 min before the ligature was tied. The severity of the arrhythmias was assessed by noting the survival, the incidence and duration of ventricular fibrillation (VF) and ventricular tachycardia (VT, defined as any run of seven or more consecutive ventricular extrasystoles) and by counting the total number of ventricular extrasystoles in the 0–30 min postligation period, as described by Clark, Foreman, Kane, McDonald & Parratt (1980).

Conscious rats

These experiments were carried out in the Institute of Pharmacology at Szeged. Male Sprague-Dawley CFY rats (150–200 g body weight) were subjected to a preliminary operation as described by Lepran, Siegmund & Szekeres (1979). Under ether anaesthesia a left thoractomy was carried out and a silk ligature placed around the left descending artery as described above. The loose ends of the ligature were pulled through a short polyethylene tube and fixed subcutaneously outside the thorax. The thorax was closed and the tube left in the thoracic cavity between the heart and the chest wall. As the chest was opened for less than 1 min, artificial respiration was not required. Penicillin was given intramuscularly on two occasions to prevent infection. A week after this preliminary operation the loose silk ends were exposed under ether anaesthesia and a pair of electrodes, introduced through a small aperture in the neck, was implanted on both sides of the chest. The animals moved freely in individual cages after the ligature had been tightened while holding the animals in the hand. Meptazinol (1 or 2 mg kg⁻¹) or saline (control group) were injected into a tail vein

15–20 min before coronary artery ligation.

In these animals the severity of the arrhythmias was assessed in the 0–20 min post ligation period by noting the survival, incidence and duration of ventricular fibrillation, ventricular tachycardia (which in these animals was defined as rates exceeding 500 min⁻¹) and of other types of arrhythmias, including extrasystoles, bigemini etc. The survival at 16 h was also noted.

Electrophysiological studies

Rats, anaesthetized with pentobarbitone sodium (60 mg kg⁻¹ i.p.) were given either meptazinol (2 mg kg⁻¹) or saline (injected into a tail vein) 15 min before excision of the left papillary muscle. The muscle was then pinned to the silastic base of a recording chamber and superfused at a rate of 10 ml/min with Krebs solution equilibrated with 95% O₂ and 5% CO₂. The composition of the Krebs solution was (mM): NaCl 119.6, NaHCO₃ 25, NaH₂PO₄ 1.2, KCl 4.7, MgCl₂ 0.57, CaCl₂ 2.5 and glucose 5.5. Temperature was maintained at 35 ± 1°C. Rectangular pulses 1 ms in duration and twice threshold voltage, delivered through a bipolar silver electrode, were used to stimulate the muscle at a frequency of 1 Hz. Transmembrane action potentials were recorded by means of conventional microelectrode techniques. The parameters measured were resting membrane potential (RMP), action potential amplitude (APA), maximum rate of depolar-

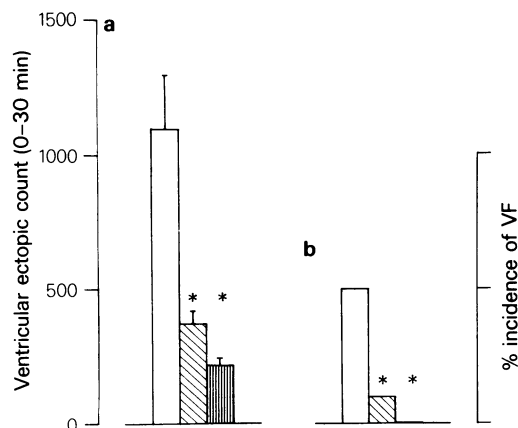


Figure 1 The mean ventricular ectopic count (a) and the percentage incidence of ventricular fibrillation (VF) (b) in the 0–30 min post ligation period in the control (open columns) and meptazinol 1 (diagonally hatched columns) and meptazinol 2 (vertically hatched columns)-treated anaesthetized rats. The number of animals in each group was 10. Vertical lines in (a) show s.e.mean. * $P < 0.05$.

ization of phase zero (MRD), and the action potential duration at both 50 and 90% repolarization (APD_{50} and APD_{90}). Recording of the action potentials was carried out after an equilibration period of 10 min and was completed within 20 min after excision.

In another series of experiments, left papillary muscles, obtained from rats killed by a blow to the head, were set up as described above. After an equilibration period of 45 min, action potentials were recorded before and 30–40 min after the cumulative addition of meptazinol, dissolved in reservoirs of gassed Krebs solution to obtain final concentrations of 4, 8 and 16 mg/l. These studies were carried out at stimulation frequencies of both 1 and 3 Hz.

Statistics

A Chi-squared test was used to analyse the statistical significance of differences in the survival and percentage incidence of arrhythmias between groups. Statistical significance of other differences between control and drug-treated groups was carried out using an unpaired or paired Student's *t* test where appropriate.

Results

Anaesthetized rats

In control rats, ligation of the main left coronary artery resulted in marked arrhythmias in the first 30 min following ligation. Although 50% of control animals had ventricular fibrillation, spontaneous reversion to sinus rhythm can occur in the rat, and mortality in this group was 30%. In the survivors, the total number of extrasystoles in the 30 min post ligation period was 1096 ± 200 (mean \pm s.e. mean) and the mean durations of the sum of periods of ventricular tachycardia and of VF were 64 ± 6 and 47 ± 3 s respectively. As can be seen in Figure 1, a significant reduction in the number of extrasystoles and in the percentage incidence of VF was achieved by the intravenous administration of meptazinol, 1 and 2 mg kg^{-1} . These doses of meptazinol also shortened the duration of VT to 18 ± 3 and 9 ± 1 s respectively and there were no deaths in the drug-treated groups. The reduction in the number of extrasystoles was especially marked in the 15–30 min post ligation period; for example 308 ± 16 ectopic beats occurred during this period in the control group compared with only 60 ± 6 and 15 ± 6 in the corresponding period in rats pretreated with meptazinol, 1 and 2 mg kg^{-1} respectively.

In the doses used, meptazinol had no effect on systemic arterial blood pressure and there were no

significant differences in the blood pressures of any of the groups immediately before coronary artery ligation ($110 \pm 7/97 \pm 6$ mmHg in the controls and $112 \pm 7/98 \pm 4$ and $104 \pm 8/93 \pm 5$ mmHg in the meptazinol-treated rats).

Conscious rats

Following 20 min of ligation, the survival in the control group of conscious rats was less than that in the corresponding anaesthetized group (31 vs 70%). This decreased survival was associated with an enhanced incidence of VF, which was usually the cause of death in the conscious rats. Figure 2 illustrates the protective effect of meptazinol (1 and 2 mg kg^{-1}) in these animals, which resulted in a decrease in the incidence of VF and consequent increase in survival at 20 min post ligation. Sixteen hours after ligation, survival was still significantly increased only in those animals given the higher dose of meptazinol (Figure 2). In the animals surviving ligation at 20 min, the time to onset of the arrhythmias was prolonged and the total duration of the arrhythmic period was reduced in the drug-treated groups (Table 1).

The changes in heart rate in the conscious rats, which survived the first 20 min of ligation, are shown in Table 2. Upon ligation, heart rate increased in the control group. In animals pretreated with meptazinol, 1 mg kg^{-1} , the heart rate changes were not as marked as in the control group and with the higher dose of drug heart rate fell slightly, but not significantly, upon ligation.

Electrophysiological studies

The most marked effect observed after *in vitro* administration of meptazinol ($4\text{--}16$ mg l^{-1}) on papillary muscle action potential characteristics was a

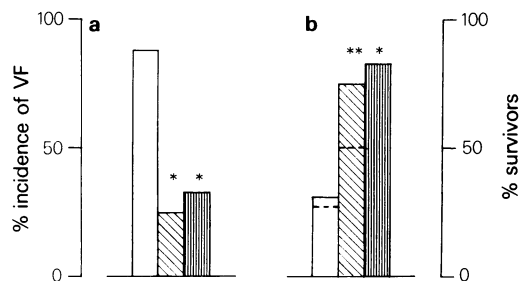


Figure 2 The percentage incidence of ventricular fibrillation (VF) (a) and of survivors at both 20 min (solid line) and at 16 h (dotted line) post-ligation (b) in conscious rats pretreated with either saline ($n = 26$, open columns) or meptazinol, 1 mg kg^{-1} ($n = 12$, diagonally hatched columns) or 2 mg kg^{-1} ($n = 12$, vertically hatched columns). * $P < 0.01$; ** $P < 0.05$.

Table 1 Effect of meptazinol on the development of arrhythmias in conscious rats having survived the acute phase of experimental myocardial infarction

| Group | n | Appearance of arrhythmias (min) | Duration of arrhythmias (min) | Length of arrhythmic attacks (s) | | | Total |
|-----------------------|----|---------------------------------|-------------------------------|----------------------------------|--------------------------|--------------------|--------------|
| | | | | Fibrillation | Tachycardia ¹ | Other ² | |
| Control | 8 | 4.8 ± 0.2 | 4.2 ± 0.8 | 12.5 ± 5.9 | 36.2 ± 5.0 | 37.5 ± 4.9 | 86.2 ± 11.3 |
| Meptazinol | | | | | | | |
| 1 mg kg ⁻¹ | 9 | 8.9 ± 1.5* | 3.4 ± 1.4 | 0.0* | 23.3 ± 12.0 | 13.3 ± 5.5** | 36.7 ± 14.0* |
| 2 mg kg ⁻¹ | 10 | 8.6 ± 1.4* | 2.7 ± 0.8 | 3.0 ± 2.1 | 12.0 ± 3.3† | 31.0 ± 8.5 | 46.0 ± 11.9* |

¹Heart rate exceeding 500 min⁻¹. ²Extrasystoles, bigemini etc.

*P < 0.05, **P < 0.01, †P < 0.001. Values shown are the means ± s.e.mean.

dose-dependent prolongation of both APD₅₀ and APD₉₀. Changes in APD₉₀ are illustrated in Figure 3, which also shows that similar effects were seen when the muscle was stimulated at either 1 or 3 Hz. The maximum rate of depolarization of phase zero (MRD) was also reduced in a dose-dependent manner by the drug but statistically significant changes were only observed at both frequencies of stimulation with the highest concentration studied (Figure 4). The resting membrane potential remained unchanged from control values of 78.4 ± 0.7 mV (1 Hz) and 74.7 ± 0.8 mV (3 Hz) following drug administration. Action potential amplitude was slightly reduced by 16 mg l⁻¹ of meptazinol at both 1 Hz (101.4 ± 0.6 vs 98.2 ± 0.9 mV) and 3 Hz (97.4 ± 1.2 vs 93.7 ± 1.6 mV).

Table 3 summarizes the action potential characteristics of papillary muscle, stimulated at 1 Hz, following excision from rats pretreated with meptazinol 2 mg kg⁻¹. As in the *in vitro* studies, meptazinol prolonged both APD₅₀ and APD₉₀. No other significant effect was observed on the parameters measured.

Discussion

These studies demonstrate that pretreatment of both conscious and anaesthetized rats with meptazinol reduces the incidence and severity of arrhythmias that occur soon after the onset of acute myocardial ischaemia ('early' arrhythmias). In anaesthetized rats there is both a reduction in ventricular ectopic activity (Figure 1) and, especially, in the serious, life-threatening arrhythmias (VT and VF). No rat so treated died as a result of coronary artery occlusion; this compares with a 30% mortality in the controls. There was also a significantly lower incidence of VF in the conscious rats pretreated with meptazinol (Figure 2) and this was almost certainly responsible for the markedly increased survival. Thus 83% of the rats given the higher dose survived up to 16 h post-occlusion compared with only 27% of the controls. These results are very similar to those previously obtained with naloxone (Fagbemi *et al.*, 1982) although meptazinol appears to be rather more active. For example, naloxone in a dose of 2 mg kg⁻¹ re-

Table 2 Alteration of heart rate in conscious rats having survived the acute phase of experimental myocardial infarction

| Group | n | Basal | Heart rate (min ⁻¹) min after coronary occlusion | | | | |
|-----------------------|----|----------|--|------------------|--------------------|-------------------|------------------|
| | | | 1 | 3 | 5 | 10 | 20 |
| Control | 8 | 356 ± 9 | 391 ± 20 (+10) | 385 ± 18 (+8) | 401 ± 15* (+13) | 394 ± 21 (+11) | 388 ± 13 (+9) |
| Meptazinol | | | | | | | |
| 1 mg kg ⁻¹ | 9 | 353 ± 19 | 359 ± 27 (+2) | 350 ± 19 (-1) | 369 ± 28 (+4) | 379 ± 20 (+7) | 361 ± 14 (+2) |
| 2 mg kg ⁻¹ | 10 | 401 ± 13 | 375 ± 21 (-6) | 387 ± 12 (-3) | 381 ± 13 (-5) | 385 ± 18 (-4) | 372 ± 12 (-7) |

*P < 0.05. % change from pre-ligation value given in parentheses.

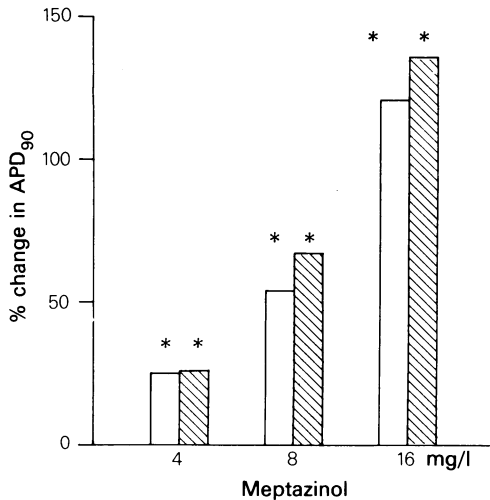


Figure 3 The percentage change in action potential duration at 90% repolarization (APD_{90}) of papillary muscle stimulated at 1 (open columns) or 3 Hz (hatched columns) and superfused with meptazinol, 4–16 mg l^{-1} . Control APD_{90} was 62.0 ± 2.2 and 45.3 ± 1.9 s at 1 and 3 Hz respectively. The number of cells measured from 4 preparations was 40 and 24 at 1 and 3 Hz respectively. * $P < 0.05$.

duced the incidence of ventricular ectopic beats from 1486 ± 171 in the controls to 454 ± 82 and the incidence of fibrillation from 50% to 10%; meptazinol in a lower dose (1 mg kg^{-1}) reduced ectopic activity from 1096 ± 200 to 375 ± 46 ventricular ectopic beats and again reduced VF from 50 to 10%.

It is probable that this protective effect of meptazinol can be explained by the marked prolongation of the ventricular muscle action potential that was observed both *in vitro* (Figure 3) and in muscle removed from rats pretreated with the drug (Table 3). This action potential prolongation was pronounced ($>40\%$) and was present at a time when protection against ventricular arrhythmias was observed (15 min after drug administration). We have

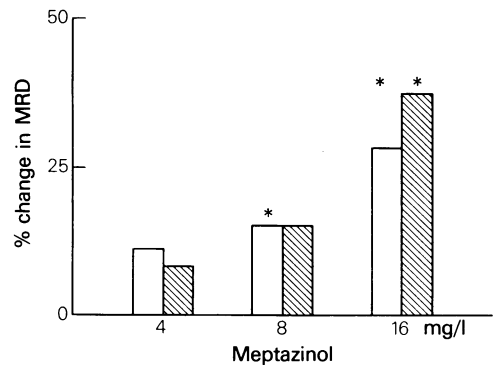


Figure 4 The percentage change in maximum rate of depolarization of phase 0 (MRD) of the action potential of papillary muscle stimulated at 1 (open columns) or 3 Hz (hatched columns) and superfused with meptazinol, 4–16 mg l^{-1} . Control MRD was 136 ± 6 and $124 \pm 7 \text{ V s}^{-1}$ at 1 and 3 Hz respectively. * $P < 0.05$.

already demonstrated that another drug, melperone, that prolongs the action potential duration of ventricular muscle (class III of Vaughan Williams' classification; Vaughan Williams, 1974) also reduces the incidence and severity of early post-occlusion arrhythmias (Kane, McDonald & Parratt, 1980). The exact ionic mechanism of this protective action of meptazinol is yet to be investigated but it is clear that, like melperone, it occurs soon after drug administration. This is in contrast to those drugs and procedures described by Vaughan Williams, when he first suggested this as a distinct mechanism of antiarrhythmic action. In these instances, action potential prolongation was only seen after prolonged drug administration (Singh & Vaughan Williams, 1970). Meptazinol, except in the highest concentration used in the *in vitro* studies (16 mg l^{-1}), had little effect on the maximum rate of depolarization. Certainly, there was no evidence for such an effect on the rapid inward Na^+ current in those studies in which papillary muscle was removed from rats pretreated with an antiarrhythmic dose of the drug (Table 3). Mep-

Table 3 Action potential characteristics of papillary muscle from rats given either saline (control) or meptazinol (2 mg kg^{-1}) intravenously 15 min before excision

| Group | n | RMP (mV) | APA (mV) | MRD (V/s) | APD_{50} (ms) | APD_{90} (ms) |
|--|----|----------------|----------------|-------------|------------------|------------------|
| Control | 49 | 76.6 ± 0.8 | 96.9 ± 0.6 | 106 ± 4 | 22.0 ± 1.0 | 56.5 ± 2.5 |
| Meptazinol 2 mg kg^{-1} i.v. | 47 | 75.8 ± 0.7 | 96.4 ± 0.7 | 100 ± 4 | $31.5 \pm 1.1^*$ | $80.2 \pm 2.7^*$ |
| % change | | | | | (+43) | (+42) |

n is the number of observations obtained from 5 papillary muscles (stimulation frequency 1 Hz) in each group.

* $P < 0.05$. Values shown are the means \pm s.e.mean.

tazinol is only a very weak local anaesthetic (Stephens *et al.*, 1978). The observed prolongation of action potential duration is, therefore, probably the basis of the reported lengthening of the effective refractory period by meptazinol (Rashid & Waterfall, 1979a, b).

The present results with meptazinol do not eliminate the possibility, raised as a consequence of our previous studies with naloxone (Fagbemi *et al.*, 1982), that an interaction with opiate receptors might be involved in the protection afforded by these drugs in the early stages of myocardial infarction. It makes more urgent a study of the possible direct electrophysiological effects of naloxone and an *in vivo* examination of the possible potential arrhythmogenic effect of endogenous opiates.

Meptazinol had minimal effects on systemic arteri-

al blood pressure and on heart rate, neither did it markedly modify the haemodynamic effects of coronary artery occlusion (see Table 2). This is in general agreement with a previously published study in cats and rats by Rashid & Waterfall (1979a). The minimal effects on respiration and on cardiovascular function, together with the marked antiarrhythmic potency demonstrated in the present studies, suggest that meptazinol would be a useful drug to employ to provide analgesia in the early stages of clinical myocardial infarction.

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