The antiarrhythmic and cardiac electrophysiological effects of buprenorphine

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1 The effects of buprenorphine, given intravenously, on the incidence and severity of early acute coronary artery occlusion-induced arrhythmias were examined in anaesthetised rats. The electrophysiological effects of buprenorphine were also examined in sheep Purkinje fibres and rat papillary muscles, superfused *in vitro* with either a normal or a hypoxic, hyperkalaemic and acidotic physiological salt solution (PSS).

2 In anaesthetised rats subjected to acute coronary artery occlusion, pretreatment with buprenorphine (1 mg kg^{-1} i.v.) markedly reduced the incidence of ventricular extra-systoles during the initial 30 min post-occlusion period. The incidence of ventricular fibrillation (VF) was also significantly reduced from 56% to 10%.

3 At the antiarrhythmic dose (1 mg kg^{-1}), buprenorphine also attenuated the sudden fall in systemic arterial blood pressure induced by acute coronary artery ligation.

4 In normal sheep Purkinje fibres and rat papillary muscles, buprenorphine (10^{-6} – 10^{-5} M) significantly reduced the action potential height and maximum rate of depolarisation of phase zero (MRD) and prolonged the duration of the action potential.

5 Superfusion of sheep Purkinje fibres and rat papillary muscles with a hypoxic, hyperkalaemic and acidotic PSS resulted in marked reductions in resting membrane potential, upstroke and duration of the action potential.

6 In the presence of the modified compared with normal PSS, buprenorphine reduced the action potential height and MRD of both sheep Purkinje fibres and rat papillary muscles to a greater extent, although its ability to prolong the action potential duration was attenuated.

7 The antiarrhythmic effects of buprenorphine observed *in vivo* may be explained by its direct cardiac electrophysiological effects. Buprenorphine might be useful in relieving pain and in reducing the severity of arrhythmias in the early stages of acute myocardial infarction.

Introduction

Since acute myocardial infarction is usually associated with severe pain it is common practice clinically to administer a narcotic analgesic. However, the opioid antagonist, naloxone, has been shown to reduce the incidence and severity of arrhythmias resulting from acute coronary artery occlusion in experimental animals (Fagbemi *et al.*, 1982; Huang *et al.*, 1986). This protective effect has also been observed with a number of other opioid antagonists. Further, this effect is stereospecific (Parratt & Sitsapesan, 1986), which suggests that the antiarrhythmic action is mediated through antagonism of the effects of endogenous opioid peptides at specific receptors. Of the three generally accepted opioid receptor subtypes (μ , κ and δ), it appears that only antagonism at the κ -receptor is associated with antiarrhythmic

activity (Mackenzie *et al.*, 1986; Sitsapesan & Parratt, 1989). It has thus been inferred that it may be more beneficial to administer an opioid with μ -agonist activity (to provide analgesia) and κ -antagonist activity (antiarrhythmic) in the early stages of acute myocardial infarction (Sitsapesan & Parratt, 1989).

The present studies were designed to evaluate the effect of buprenorphine, a compound with partial μ -agonist/ κ -antagonist activity (Richards & Sadee, 1985; Takemori *et al.*, 1986) on the incidence and severity of early arrhythmias associated with acute coronary artery occlusion in anaesthetised rats. In order to elucidate further the possible mechanisms involved, the cardiac electrophysiological effects of buprenorphine were also studied *in vitro* in normal

sheep Purkinje fibres and rat ventricular muscles and in similar preparations exposed to conditions that mimic mild myocardial ischaemia (Boachie-Ansah *et al.*, 1989).

Methods

Anaesthetised rats

Male Sprague-Dawley rats (250–400 g body weight) were anaesthetised with pentobarbitone sodium (60 mg kg^{-1} , i.p.). The trachea and femoral vein were cannulated to allow artificial respiration and drug administration, respectively. Systemic arterial blood pressure was monitored via a catheter placed in the carotid artery, and recorded, together with a standard lead I ECG, by use of a Mingograf 82 ink-jet recorder (Elema Schonander). 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. Artificial ventilation with room air (stroke volume $1.5 \text{ ml } 100 \text{ g}^{-1}$; rate $54 \text{ beats min}^{-1}$) was commenced immediately to maintain normal arterial PO_2 , PCO_2 , and pH parameters. After the pericardium had been incised, the heart was exteriorized and a 6/0 braided silk suture was placed under the left main coronary artery. The heart was repositioned in the thoracic cavity and the animal left to recover for 15 min.

Buprenorphine (0.01, 0.1 and 1.0 mg kg^{-1}) or saline was administered intravenously and after another 15 min the ligature was tied. The severity of the resulting arrhythmias was assessed by counting the total number of ventricular extrasystoles occurring during the 0–30 min postligation period and by computing the mortality rate as well as the incidence and duration of ventricular fibrillation (VF) and ventricular tachycardia (VT, defined as any run of six or more consecutive ventricular extrasystoles), as described by Clark *et al.* (1980).

Electrophysiological studies

Experiments were performed on both sheep cardiac Purkinje fibres and rat papillary muscles superfused *in vitro* with either a normal physiological salt solution (PSS) or a modified PSS (i.e., a hypoxic, hyperkalaemic, and acidotic solution).

Sheep Purkinje fibres Sheep hearts were collected from a local abattoir and delivered to the laboratory in cooled normal PSS within 30 min of excision. Free-running Purkinje fibres were dissected and pinned to the silastic base of a recording chamber

and superfused at a rate of 5 ml min^{-1} with normal PSS equilibrated with 95% O_2 /5% CO_2 at a temperature of $36.5 \pm 0.5^\circ\text{C}$. The composition of the normal PSS was as follows (mm): NaCl 125, NaHCO_3 25, NaH_2PO_4 1.2, MgCl_2 1.0, KCl 5.4, CaCl_2 1.8, glucose 5.5. That of the modified PSS was as follows (mm): NaCl 141.5, NaHCO_3 8.5, NaH_2PO_4 1.2, MgCl_2 1.0, KCl 8.0, CaCl_2 1.8, glucose 5.5. The modified solution was equilibrated with 95% N_2 /5% CO_2 to yield a PO_2 and a pH in the organ bath of $34.1 \pm 0.6 \text{ mmHg}$ and 6.8 ± 0.01 units, respectively, compared with values in normal PSS of $419 \pm 31 \text{ mmHg}$ and 7.31 ± 0.02 units.

Rat papillary muscles Male Sprague-Dawley rats (250–350 g body weight) were stunned and their hearts quickly removed and placed in cold normal PSS. Left papillary muscles were excised and mounted in a recording chamber as above and superfused at a rate of 10 ml min^{-1} with normal PSS equilibrated with 95% O_2 /5% CO_2 at a temperature of $34.5 \pm 0.5^\circ\text{C}$. The compositions of the normal and modified PSS used were the same as above except for (mm): CaCl_2 2.5, glucose 11.0. The modified PSS was gassed with 95% N_2 /5% CO_2 to yield a bath PO_2 and pH in the ranges described above for sheep Purkinje fibres.

Rectangular pulses 1 ms in duration and twice threshold voltage, delivered through a bipolar silver electrode, were used to stimulate both preparations at a rate of 1.5 Hz. Transmembrane action potentials were recorded using conventional microelectrode techniques. The variables measured were resting membrane potential (RMP); action potential amplitude (APA); the maximum rate of depolarization of phase zero (MRD), which was determined by an electronic differentiating circuit; the action potential duration at 50 and 90% repolarisation levels (APD_{50} and APD_{90}). In all cases, the preparations were allowed to equilibrate in normal PSS for 1–2 h before exposure to the modified PSS or drug.

Experimental protocol

To observe drug effects on normal preparations, 6–10 action potentials were recorded before and 30–40 min after cumulative addition of buprenorphine, which was dissolved in reservoirs of gassed normal PSS to obtain final bath concentrations detailed below. In a different set of preparations, the effects of the modified PSS alone were studied by recording multiple action potentials before and at 30, 60, 90, and 120 min following exposure to the modified PSS. To observe drug-induced effects in the presence of the modified PSS, other preparations were used; action potentials were recorded before and 30 min

Table 1 Effect of buprenorphine on the incidence and severity of early arrhythmias resulting from acute coronary artery occlusion in anaesthetized rats

Treatment	n	Ventricular ectopic beats	Ventricular tachycardia (VT)		Ventricular fibrillation (VF)		Mortality (%)
			Duration (s)	Incidence (%)	Duration (s)	Incidence (%)	
Control	27	1518 ± 190	102.1 ± 17.8	100	22.8 ± 18.2	56	22
Buprenorphine							
0.01 mg kg ⁻¹	10	1617 ± 398	96.1 ± 24.7	100	2.2	30	20
0.1 mg kg ⁻¹	19	1049 ± 189	74.6 ± 18.5	100	37.6 ± 15.9	21	0
1.0 mg kg ⁻¹	20	692 ± 128**	43.9 ± 11	85	34.2 ± 33.2	10*	5

Values are expressed as means ± s.e.mean.

* $P < 0.025$, ** $P < 0.005$, significantly different from value in control group. Ventricular ectopic beats and the durations of VT and VF were counted in survivors only.

after superfusion with the modified solution alone, and subsequently after the administration of two cumulative concentrations of buprenorphine dissolved in modified PSS.

Analysis of data

Data from the electrophysiological studies are expressed either as mean values ± s.e.mean or mean percentage change from control values ± s.e.mean. In both the anaesthetised rat and electrophysiological studies, multiple treatment and control means were analysed by use of a one-way analysis of variance and, where the F-value permitted further analysis, individual treatment means were compared with respective control values by a Modified *t* test. A Chi-squared test was used to compare the % incidences of ventricular tachycardia (VT) and fibrillation (VF), and mortality in control and treatment groups. In all other comparisons an unpaired or paired Student's *t* test (two-tailed) was employed

as appropriate. $P < 0.05$ was considered to be statistically significant.

Results

Anaesthetised rats

In control rats, acute occlusion of the left main coronary artery resulted in marked ectopic activity in the initial 30 min post-ligation period. As shown in Table 1, 56% of control animals had ventricular fibrillation (VF); only 22% died as a result of VF because of the ability of the rat heart to revert spontaneously to normal sinus rhythm. Intravenous administration of buprenorphine, 1 mg kg⁻¹, resulted in significant reductions in both the total number of extrasystoles and the percentage incidence of VF,

Table 2 Effects of buprenorphine on mean arterial blood pressure in anaesthetized rats subjected to acute coronary artery occlusion

Treatment	n	Pre-drug	Pre-ligation	Post-ligation (min)			
				1	5	15	30
Control	21	86 ± 3	94 ± 3†	68 ± 3	77 ± 3	87 ± 5	82 ± 4
Buprenorphine							
0.01 mg kg ⁻¹	8	83 ± 2	104 ± 6†	66 ± 6	78 ± 10	78 ± 9	83 ± 9
0.1 mg kg ⁻¹	19	86 ± 3	101 ± 4†	89 ± 5*	89 ± 6	84 ± 4	78 ± 5
1.0 mg kg ⁻¹	19	88 ± 4	107 ± 6†	97 ± 4*	92 ± 6*	92 ± 5	87 ± 5

Values are expressed as means ± s.e.mean.

† $P < 0.05$ significantly different from pre-drug value.

* $P < 0.05$ significantly different from value in control group.

and tended also to reduce the duration of ventricular tachycardia (VT) (Table 1). The two lower doses of buprenorphine, 0.01 and 0.1 mg kg⁻¹, did not cause statistically significant differences in any of the arrhythmic indices, although the latter dose did tend to reduce the total ectopic count and the incidence of VF.

The effects of buprenorphine and of coronary artery occlusion on mean arterial blood pressure are summarised in Table 2. In the doses used, buprenorphine only tended to elevate systemic arterial blood pressure during the pre-ligation period. In control rats, acute coronary artery occlusion caused an immediate fall in blood pressure followed by a slow recovery towards pre-ligation levels. Buprenorphine, 0.1 and 1.0 mg kg⁻¹, attenuated this immediate fall in blood pressure (reductions of 12% and 9%, respectively, compared with 28% in controls). Heart rate was not significantly changed from the control value of 411 ± 16 beats min⁻¹ by coronary artery occlusion or by buprenorphine in the concentrations used.

Electrophysiological studies

Sheep Purkinje fibres The effects of buprenorphine (10⁻⁸–10⁻⁵ M) on normal sheep Purkinje action potentials are summarised in Table 3. Buprenorphine (10⁻⁶–10⁻⁵ M) caused significant concentration-dependent reductions in the maximum rate of depolarisation of phase zero (MRD) without modifying the resting membrane potential. At the highest concentration used (10⁻⁵ M), buprenorphine also reduced the amplitude of the action potential (APA) and prolonged the action potential duration at 90% repolarisation (APD₉₀).

Figure 1 shows the effects of superfusing sheep Purkinje fibres either with the modified PSS alone or that containing buprenorphine (10⁻⁶ and

Figure 1 Percentage changes (from control values) in sheep Purkinje action potential characteristics induced by modified PSS alone (unbroken line) and modified PSS plus buprenorphine (Bupr), 10⁻⁶ and 5 × 10⁻⁶ M (broken line). *Significantly different from value in modified PSS alone. *n* = 5–8. RMP = resting membrane potential, MRD = maximum rate of depolarisation of phase zero, APA = action potential amplitude, APD₅₀ and APD₉₀ = action potential duration at 50% and 90% repolarisation, respectively.

5 × 10⁻⁶ M). Within 30 min of exposure, the hypoxic, hyperkalaemic and acidotic PSS had reduced significantly all of the measured variables. There were no further significant reductions in these variables during the 30–120 min exposure period to the modified PSS alone. When given after the first 30 min of exposure to the modified PSS, buprenorphine (10⁻⁶ and 5 × 10⁻⁶ M) reduced both the MRD and APA of the depressed action potentials without affecting the resting membrane potential or action potential duration (Figure 1). Thus, as illustrated in Figure 2, under ischaemic compared to normal conditions, buprenorphine had a greater depressant effect on the

Table 3 The % changes induced by buprenorphine (10⁻⁸ to 10⁻⁵ M) in action potential characteristics of normal sheep Purkinje fibres

	Control	% change after buprenorphine (M)				
		10 ⁻⁸	10 ⁻⁷	10 ⁻⁶	5 × 10 ⁻⁶	10 ⁻⁵
RMP (mV)	-83.3 ± 1.6	-0.2 ± 0.6	-0.4 ± 0.9	-0.2 ± 0.5	-2.4 ± 0.7	-3.2 ± 0.7
MRD (V s ⁻¹)	487 ± 16	-1.0 ± 1.6	-4.3 ± 2.7	-10.6 ± 4.1*	-20.8 ± 3.2*	-60.2 ± 7.8*
APA (mV)	114.4 ± 2.2	-0.3 ± 0.8	-0.6 ± 1.1	-1.9 ± 0.5	-6.2 ± 1.5	-25.0 ± 2.9*
APD ₅₀ (ms)	140.4 ± 13.6	-1.3 ± 2.4	-2.9 ± 2.2	+1.0 ± 3.1	-0.1 ± 2.6	+6.6 ± 6.7
APD ₉₀ (ms)	231.4 ± 14.2	+1.0 ± 2.2	+1.4 ± 2.2	+6.2 ± 3.2	+10.9 ± 4.0	+25.0 ± 6.8*

Values shown are mean ± s.e.mean, *n* = 6.

* *P* < 0.05 significantly different from zero. Abbreviations are: RMP = resting membrane potential; MRD = maximum rate of depolarisation of phase zero; APA = action potential amplitude; APD₅₀ and APD₉₀ = action potential duration at 50% and 90% repolarisation, respectively.

Figure 2 The percentage reduction in (a) maximum rate of depolarisation (MRD) and in (b) action potential duration (APD₉₀) of sheep Purkinje fibres caused by buprenorphine (Bupr), 10⁻⁶ and 5 × 10⁻⁶ M, dissolved either in normal (stippled columns) or modified (open columns PSS). *n* = 5–6. **P* < 0.05, significantly different from effect in normal PSS.

upstroke of the action potential but failed to prolong APD₉₀.

Rat ventricular muscle On normal rat papillary muscle, the most marked effect of buprenorphine (10⁻⁶–10⁻⁵ M) was a concentration-dependent prolongation of APD₉₀. Increases in APD₉₀ of 8 ± 3%, 11 ± 2% (*P* < 0.05) and 22 ± 3% (*P* < 0.05) above the control value of 94.8 ± 4.1 ms were observed following superfusion with 10⁻⁶, 5 × 10⁻⁶ and 10⁻⁵ M buprenorphine, respectively. In these concentrations, buprenorphine also reduced significantly the action potential amplitude (from 100.7 ± 1.2 to 94.6 ± 0.9 mV) and tended to reduce MRD (from 117.5 ± 5 to 109 ± 2 V s⁻¹).

Exposure of rat papillary muscle to the modified PSS alone had similar effects to those observed in the sheep Purkinje fibres. However, as can be seen in Table 4, although the changes in RMP, MRD and APA were maximal by 30 min, those in the APD were not. Both APD₅₀ and APD₉₀ of the rat ventricular muscle continued to decline throughout the 2 h of exposure to the 'ischaemic' solution. Buprenorphine, 10⁻⁵ M, prevented this decline in APD₅₀ and APD₉₀, the respective values in the presence of the drug being 21.8 ± 1.3 and 45.6 ± 2.4 ms. Under ischaemic conditions, buprenorphine (5 × 10⁻⁶ and 10⁻⁵ M) also decreased the MRD and APA without modifying the resting membrane potential. As was observed in Purkinje tissue, this effect of buprenorphine was more marked in the presence of the modified PSS (Figure 3).

Discussion

The results of these studies demonstrate that pretreatment of anaesthetized rats with buprenorphine reduces the incidence and severity of the early

Table 4 The effects of the 'ischaemic' (i.e. hypoxic, hyperkalaemic, and acidotic) physiological salt solution on action potential characteristics of rat ventricular muscle paced at 1.5 Hz

	Control	30	Time 'post-ischaemia' (min)		
			60	90	120
RMP (mV)	-78.9 ± 0.8	-67.6 ± 0.6*	-69.5 ± 1.2*	-68.2 ± 0.8*	-68.8 ± 0.7*
MRD (V s ⁻¹)	165 ± 8	99 ± 10*	101 ± 7*	98 ± 9*	96 ± 10*
APA (mV)	105.1 ± 1.8	88.6 ± 1.6*	88.2 ± 2.3*	85.7 ± 2.4*	85.0 ± 2.6*
APD ₅₀ (ms)	21.1 ± 1.1	21.8 ± 0.8	19.0 ± 1.7	17.9 ± 1.6	16.6 ± 1.5
APD ₉₀ (ms)	70.3 ± 3.5	49.9 ± 3.4*	41.3 ± 3.4*,†	38.6 ± 3.6*,†	35.6 ± 3.1*,†

Values shown are mean ± s.e.mean, *n* = 6.

* *P* < 0.05 significantly different from control value.

† *P* < 0.05 significantly different value at 30 min post-ischaemia. For abbreviations used see Table 3.

Figure 3 The percentage reduction in the maximum rate of depolarisation (MRD) of rat papillary muscle caused by buprenorphine (Bupr), 5×10^{-6} and 10^{-5} M, dissolved in normal (stippled columns) or modified (open columns) PSS. $n = 5-6$. * $P < 0.05$, significantly different from effect in normal PSS.

arrhythmias resulting from acute myocardial ischaemia. Further, buprenorphine, in micromolar concentrations, exerts direct effects on the electrophysiological characteristics of normal cardiac tissues and of cardiac tissues exposed *in vitro* to conditions that mimic mild myocardial ischaemia.

The protective effects of buprenorphine against these early ischaemia-induced arrhythmias are similar to those observed for the opioid receptor antagonist, naloxone, and the opioid agonist/antagonist, meptazinol (Fagbemi *et al.*, 1982; 1983). Recent binding studies in the rat indicate that buprenorphine achieves about 50% occupancy of both μ - and κ -opioid receptor sites at doses around $30 \mu\text{g kg}^{-1}$, and saturates both sites *in vivo* at $250-500 \mu\text{g kg}^{-1}$ (Sadée *et al.*, 1983). Therefore, the present finding that buprenorphine, at a dose of 1 mg kg^{-1} , suppresses early ischaemic arrhythmias raises the possibility that this antiarrhythmic effect may be related or secondary to its opioid receptor occupancy. These antiarrhythmic effects were not associated with marked haemodynamic effects, apart from a slight attenuation of the acute ligation-induced fall in arterial blood pressure. The mechanism underlying this effect is not known, although the finding that diamorphine produces a similar effect in anesthetized rats (R. Sitsapasan, unpublished observations) would tend to suggest μ -receptor acti-

vation as a possible basis. Unlike buprenorphine, however, the diamorphine effect was not associated with any protection against early ischaemic arrhythmias (R. Sitsapasan, unpublished observations). Thus, it is unlikely that this effect on blood pressure is responsible for the antiarrhythmic effects of buprenorphine.

Buprenorphine also exerted effects on the electrophysiological characteristics of normal sheep Purkinje and rat ventricular tissues *in vitro*, reducing both the maximum rate of depolarization and action potential height and prolonging the action potential duration. The depressant effects on MRD and action potential amplitude may be due to blockade of fast Na^+ channels, the opening of which are responsible for the upstroke of action potential in Purkinje and ventricular tissue. The mechanism underlying the action potential prolongation, however, remains unknown. The fact that this effect was more pronounced on terminal repolarisation suggests a possible block of delayed outward K^+ conductance, but further studies are required to provide a definitive answer. The above effects of buprenorphine are qualitatively similar to those obtained for naloxone and meptazinol on guinea-pig and rat ventricular muscles *in vitro* (Fagbemi *et al.*, 1983; Brasch, 1986).

The changes induced by the modified PSS in sheep Purkinje and rat ventricular action potential characteristics, namely, marked reductions in resting membrane potential, maximum rate of depolarization of phase 0, action potential amplitude and action potential duration, are similar to those described previously in isolated cardiac tissues (Gilmour & Zipes, 1980; Evans *et al.*, 1984) and during mild myocardial ischaemia *in vivo* (Downar *et al.*, 1977). Evidence suggests that these changes are due largely to the elevated extracellular K^+ concentration, with some less major contribution from the concomitant hypoxia and acidosis (Boachie-Ansah *et al.*, 1989). The changes remained relatively stable during the 30-120 min exposure period, thus allowing evaluation of drug action on depressed fast responses to be carried out. The continued, steady reductions in rat ventricular action potential duration, induced by the prolonged exposure to the modified PSS, have also been observed in rabbit ventricular muscles (G. Boachie-Ansah, unpublished observations) and may be due to the greater susceptibility of ventricular tissue to prolonged hypoxia (Fozzard, 1975; Wit & Bigger, 1975).

In the presence of the modified PSS, buprenorphine caused more marked reductions in the MRD and action potential amplitude in both sheep Purkinje and rat ventricular tissue and prevented the steady decline in rat ventricular action potential duration. The ability to prolong sheep Purkinje action potentials was, however, virtually lost under

simulated ischaemic conditions. The potentiation of the depressant effect of buprenorphine on phase zero of the action potential may be due to the membrane depolarization induced by the modified PSS and suggests that buprenorphine, like other antiarrhythmic drugs such as lignocaine, preferentially blocks the inactivated form of the fast Na^+ channel (Hondeghe & Katzung, 1984). The mechanism(s) underlying the apparent loss or attenuation of the ability of buprenorphine to prolong sheep Purkinje action potential under conditions that mimicked myocardial ischaemia is not clear. If prolongation of the action potential duration by buprenorphine is mediated via blockade of the outward K^+ current as suggested, then it is possible that this effect was swamped by the opposing actions of hypoxia and elevated K^+ to increase K^+ conductance.

It is possible that the cardiac electrophysiological effects of buprenorphine described in these studies (depression of the MRD and action potential height and prolongation of the action potential duration) are responsible for the observed protective effect of buprenorphine *in vivo*. The ability to block fast Na^+ channels (leading to depression of MRD), especially in depolarized tissue, is thought to be responsible for the antiarrhythmic actions of the Class I antiarrhythmic drugs such as lignocaine (Vaughan Williams, 1980; Carmeliet, 1984). Similarly, prolongation of the duration of the cardiac action potential is thought to be the basis of the antiarrhythmic actions of the Class III antiarrhythmic drugs like amiodarone (Vaughan Williams, 1980). Furthermore, drugs possessing either of these properties have been shown to suppress occlusion-induced arrhythmias in anaesthetised rats (Botting *et al.*, 1985).

It remains to be resolved, however, whether the observed antiarrhythmic and cardiac electrophysiological effects of buprenorphine are, indeed, mediated via specific opioid receptor activation. The rather high concentration (1 mg kg^{-1}) required to confer protection against ischaemic arrhythmias would tend to rule out the possible involvement of specific opioid receptor activation. However, there is increasing evidence that, unlike the antagonism of exogenously administered opioid receptor agonists, effective antagonism of endogenous opioid systems may require much higher concentrations of opioid

receptor antagonists (i.e., in the mg kg^{-1} range; Cohen *et al.*, 1982). Furthermore, the antiarrhythmic activity of several opioid receptor antagonists has been shown to be stereospecific in the rat model, notwithstanding the fact that high concentrations ($1\text{--}3 \text{ mg kg}^{-1}$) of drug were required to confer protection (Parratt & Sitsapesan, 1986). Thus, the possibility still exists that the antiarrhythmic actions of buprenorphine were mediated via opioid receptors, although it is not possible to specify which receptor subtype(s) are involved from the present study.

The equally high concentrations ($10^{-6}\text{--}10^{-5} \text{ M}$) of buprenorphine required to modify cardiac action potential characteristics could also be used to argue against the possible involvement of opioid receptor activation. In this respect, it is of interest to note that even higher concentrations ($3\text{--}120 \times 10^{-6} \text{ M}$) of naloxone were required to produce similar effects on guinea-pig atrial ventricular action potentials and that the effects of naloxone were not stereospecific (Brasch, 1986), which suggests that they are not mediated via opioid receptor activation. It is not known, however, whether the buprenorphine effects are similarly non-stereospecific. Thus, further studies would be required to address the issue of the possible relationship of specific opioid receptor activation to the antiarrhythmic and cardiac electrophysiological effects of buprenorphine.

In summary, buprenorphine afforded protection against early ischaemia-induced arrhythmias in anaesthetised rats. In normally-polarized sheep Purkinje fibres and rat papillary muscles, buprenorphine reduced the action potential amplitude and maximum rate of depolarisation of phase zero and prolonged the action potential duration. In both sheep Purkinje fibres and rat papillary muscles exposed to combined hypoxia, hyperkalaemia and acidosis, the ability of buprenorphine to depress the action potential amplitude and maximum rate of depolarization of phase zero was enhanced, whereas its ability to prolong the action potential duration was attenuated. It is suggested that these cardiac electrophysiological actions may underlie the observed antiarrhythmic activity of buprenorphine *in vivo*. Further, buprenorphine might serve the useful dual purpose of relieving pain and reducing the severity of arrhythmias in the early stages of acute myocardial infarction.

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