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Cardiovascular actions of the κ-agonist, U-50,488H, in the absence and presence of opioid receptor blockade

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1 The cardiovascular actions of U-50,488H, a κ-receptor agonist, were studied in rat isolated perfused hearts, and in anaesthetized rats, over concentrations or doses generally above those required to produce κ-receptor-mediated effects.

2 U-50,488H dose-dependently decreased left-ventricular peak systolic pressure and beating rate *in vitro* and reduced blood pressure and heart rate *in vivo*.

3 Over the concentration range of 1–30 μM *in vitro*, and the dose-range of 0.5–32 μmol kg^{-1} *in vivo*, U-50,488H prolonged the P–R, QRS and Q–T intervals of the ECG.

4 The effects of U-50,488H were not antagonized by an opioid receptor antagonist, naloxone (1 μM or 8 μmol kg^{-1}). Similarly, the opioid receptor antagonist, MR 2266, at 8 μmol kg^{-1} did not significantly reduce the cardiovascular actions of U-50,488H *in vivo*.

5 The actions of U-50,488H on responses to electrical stimulation were also studied. Over the dose range of 0.5–32 μmol kg^{-1}, U-50,488H altered thresholds and effective refractory period. It had a biphasic action on thresholds for induction of ventricular fibrillation. Thresholds were decreased at lower doses (0.5–4 μmol kg^{-1}) but increased at higher doses (8–32 μmol kg^{-1}). The effects of lower doses were blocked by naloxone. Effective refractory period and threshold pulse width only increased with dose.

6 In conclusion, U-50,488H at high concentration, had direct depressant actions on cardiac contractility, electrical excitability and the ECG. These depressant effects were not antagonized by the opioid receptor antagonists, naloxone and MR 2266, and probably do not involve opioid receptors. Furthermore, some of the observed effects were those expected to result from sodium channel blockade.

Keywords: U-50,488H; ECG; electrical stimulation; sodium channel blockade; naloxone; MR 2266; rat hearts

Introduction

U-50,488H, a selective κ-receptor agonist (Lahti *et al.*, 1982), has been shown to induce ventricular arrhythmias in the isolated perfused heart of the rat when given as a bolus of 44 or 132 nmol (Wong *et al.*, 1990). Further, the incidence and severity of ischaemia and reperfusion-induced arrhythmias are reduced by the opioid receptor antagonists naloxone (Sarne *et al.*, 1991) and MR 2266 (Wong *et al.*, 1990). Other studies suggest that κ-receptor blockade may be antiarrhythmic (Sitsapesan & Parratt, 1989) whereas buprenorphine, an agent with mixed actions on μ- and κ-receptors, may exert antiarrhythmic effects directly, independent of opioid receptors (Boachie-Ansah *et al.*, 1989). In view of the possibility that U-50,488H has direct cardiac effects, as well as the fact that the bolus doses used by Wong *et al.* (1990) may have produced transient high concentrations, we decided to extend that study. We used a wide range of steady state concentrations and compared effects *in vitro* with those *in vivo* to determine whether the former actions could be observed in intact animals.

U-50,488H has recently been shown to exert sodium channel blocking actions in neuronal tissue; actions which are not reversed by opioid receptor antagonists (Alzheimer & Ten Bruggencate, 1990). It thus appeared useful to examine U-50,488H for cardiovascular actions which could relate to sodium channel blocking actions in cardiac tissue and to use naloxone to block possible opioid-receptor-mediated effects so revealing direct cardiac effects.

Known sodium channel blockers *in vivo* depress blood pressure and heart rate, prolong P–R and QRS intervals and depress electrical excitability. Concentrations *in vitro* corresponding to effective plasma concentrations *in vivo* depress contractility, lower heart rate and widen P–R and QRS intervals in rat isolated hearts (Walker & Beatch, 1988; Abraham *et al.*, 1989; Howard & Walker, 1990). Such concentrations also depress the rise rate of phase 0 of intracellular action potentials.

We have systematically investigated the actions of U-50,488H in rat isolated hearts and in pentobarbitone-anaesthetized rats. We assessed the effects of U-50,488H on left-ventricular peak systolic pressure, heart rate and the ECG *in vitro*. *In vivo*, blood pressure, heart rate and the ECG effects were examined together with sensitivity to electrical stimulation of the left ventricle. Results suggested that, at concentrations or doses greater than those required to produce agonism at κ-receptors, U-50,488H blocked sodium channels in rat heart.

Methods

Male Sprague-Dawley rats (150–350 g) were used in accordance with the guidelines of the University of British Columbia's Animal Care Committee. Intact rats were anaesthetized with pentobarbitone (60 mg kg^{-1}, i.p.). When required, the trachea was cannulated for artificial ventilation at a stroke volume of 10 ml kg^{-1}, 60 strokes min^{-1}. Body temperature was monitored by rectal thermometer and maintained between 36–37°C with a heating lamp.

Isolated hearts

The procedure described by Curtis *et al.* (1986) was used. Rats were killed and their hearts excised for immediate perfusion with cold Krebs-Henseleit solution. Thereafter they were mounted on a modified Langendorff apparatus (Curtis *et al.*, 1986) and perfused at a constant pressure of 100 mmHg with oxygenated Krebs-Henseleit solution (pH 7.4), and at a temperature of 37°C.

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The left atrium was removed and a compliant balloon inserted into the left ventricle. The end diastolic pressure in the balloon was adjusted to 10 mmHg with approximately 0.5 ml of saline. Pressures within the balloon were monitored on a Grass Polygraph (model 7D) while the maximum rate of intraventricular pressure development ($+dp.dt^{-1}_{max}$) was obtained with a Grass differentiator (model 7P20C).

The ECG was recorded via two atraumatic silver-ball electrodes placed on the epicardial surface of the right atrium and left ventricle, respectively. The ECG was recorded on a Grass Polygraph at a bandwidth of 0.1–40 Hz. All hearts were of similar weight (1.2–1.6 g).

A random block design was used to assign hearts to the following groups: saline, and U-50,488H (at 1, 3, 10 and 30 μM for 10 min each) in the presence or absence of 1 μM naloxone, a concentration at least 100× the pA_2 (Martin, 1983). Hearts were left to stabilize for 10 min before addition of saline vehicle, or naloxone, 10 min prior to dosing with U-50,488H.

In vivo *effects of U-50,488H*

In pentobarbitone-anaesthetized, and artificially ventilated rats ($n = 6$ per group), the left carotid artery and right jugular vein were cannulated. Dose-response curves were constructed for U-50,488H with cumulative doses of 0.5, 1.0, 2.0, 4.0, 8.0, 16.0 and 32.0 μmol kg^{-1} i.v. Each dose was infused over 2 min and the blood pressure, heart rate and ECG were recorded 10 min later, just before addition of the next dose.

In a separate experiment, and according to a random and blind design, either saline, naloxone (8 μmol kg^{-1}) or MR 2266 (8 μmol kg^{-1}) was administered before giving U-50,488H at 16 μmol kg^{-1}. All rats were allowed to stabilize for 10 min before receiving the first injection of saline, or either of the two opioid antagonists. The dose of U-50,488H was chosen from the previous dose-response study as one that produced significant, but not maximal, responses which could be expected to be blocked completely by the high doses of antagonists used. We performed an initial *in vivo* trial study with naloxone and the dose we decided to use was the highest dose without effect on the ECG, blood pressure or heart rate and much higher than the pA_2 (Martin, 1983). This chosen dose could be expected to block effectively any opioid receptor-dependent effects of U-50,488H, even at the highest doses.

Electrical stimulation studies

In pentobarbitone-anaesthetized rats the left-carotid artery and right jugular vein were cannulated. Two Teflon-coated silver wire stimulating-electrodes were inserted through the chest wall and implanted in the left ventricle (Walker & Beatch, 1988). The inter-electrode distance was approximately 1 mm and square wave stimulation was used to determine: threshold current for capture (iT–μA), threshold pulse width for capture (tT–ms), maximum following frequency (MMF–Hz), ventricular fibrillation threshold (VFt–μA) and effective refractory period (ERP–ms) according to previously described methods (Howard & Walker, 1990).

The variables iT and tT approximate to the rheobase and chronaxie, respectively, of the i vs t curve and are a measure of sodium channel availability. Unfortunately, since iT and tT cannot be measured under rigidly controlled conditions they are imperfect measures. ERP and MFF are related such that it might be expected that MFF(Hz) = 1000/ERP(ms). However, although the two are similar they are sufficiently different to warrant reporting both. Thus while ERP, as measured, is a reasonable measure of effective refractive period, MFF is more a measure of relative refractory period, and ventricular functional refractory period, and thus can exhibit a different sensitivity to drugs from ERP. The process of determination of MFF, namely a steadily increasing frequency of stimulation, can be associated with accumulation of extracellular K^+ thereby adding an extra component to what would otherwise be another measure of ERP. MFF and ERP are not equally sensitive to frequency-dependent sodium channel blockers (Walker & Beatch, 1988). Stimulation studies were performed only *in vivo* since results are more predictable in the intact animal than in isolated hearts. The full profile of U50,488H on the various stimulation variables is given here to allow for comparison with the profiles obtained for other Class 1 anti-arrhythmic drugs (e.g. as in Abraham *et al.*, 1989).

The stimulation variables were determined 5 min after each dose of saline, or U-50,488H, in the absence or presence of a single previous dose (8 μmol kg^{-1}) of naloxone. U-50,488H was given cumulatively at 0.5, 1.0, 2.0, 4.0, 8.0, 16.0 and 32.0 μmol kg^{-1}.

Drugs

The drugs used were: U-50,488H (trans-(±)-3,4-dichloro-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-benzene-acetamide methane sulphonate), naloxone and MR 2266 ((−)-5,9-alpha-diethyl)-2-(3-furylmethyl-2′-hydroxy-6,7-benzomorphan). U-50,488H and MR 2266 were generous gifts from the Upjohn Company and Boehringer Ingelheim (Canada) Ltd., respectively. Naloxone hydrochloride was purchased from DuPont Pharmaceutical Co. All drugs were prepared as stock solutions dissolved in a 0.9% NaCl solution for *in vivo* studies. Drugs were dissolved in Krebs-Henseleit for *in vitro* studies.

Statistical analysis

Statistical analyses were performed with the NCSS statistical package (Hintze, 1987) and values are presented as mean ± s.e.mean. General Linear Model ANOVA was used for balanced studies and multiple comparisons made by Duncan's test. A difference at $P < 0.05$ was considered significant. The effects of U-50,488H are expressed as changes from the pre-U-50,488H value in the absence, or presence, of naloxone. Two types of statistical comparisons were made. With 'raw' data, simple comparisons of means were made. However, in dose-response studies, the mean percentage changes induced by different doses of U50,488H were compared with zero in a manner analogous to that used in t tests for differences.

Results

Figure 1 shows the effects of U-50,488H on peak systolic left ventricular pressure and heart rate in terms of changes from the pre-U-50,488H values in isolated hearts. Corresponding changes in ECG intervals recorded from rat isolated perfused hearts are shown in Figure 2.

U-50,488H dose-dependently reduced peak-systolic left ventricular pressure and heart rate, while the maximum rate of intra-ventricular pressure development ($+dp.dt^{-1}_{max}$) was also reduced (data not shown). It also dose-dependently prolonged both P–R interval and QRS duration. All of the above effects were still present in the presence of 1 μM naloxone. The only notable difference between the dose-response curves in the presence or absence of naloxone was for a tendency for higher peak systolic pressure in the presence of naloxone. The effects of naloxone on isolated hearts were not statistically different from those of saline alone.

In intact pentobarbitone-anaesthetized rats, U-50,488H dose-dependently lowered both blood pressure and heart rate (Figure 3a). In addition, it prolonged the P–R and Q–T intervals and widened the QRS complex in a dose-dependent manner (Figure 3b). In both Figure 3a and b changes from pre-drug values are shown. Statistically significant depression of blood pressure and heart rate occurred after 0.5 μmol kg^{-1} whereas larger doses (2–4 μmol kg^{-1}) had to be given before statistically significant changes were seen in P–R interval and QRS width. In the separate experiment summarized in Table 1, blood pressure, heart rate and ECG changes induced by 16 μmol kg^{-1} U-50,488H were not prevented by pretreatment

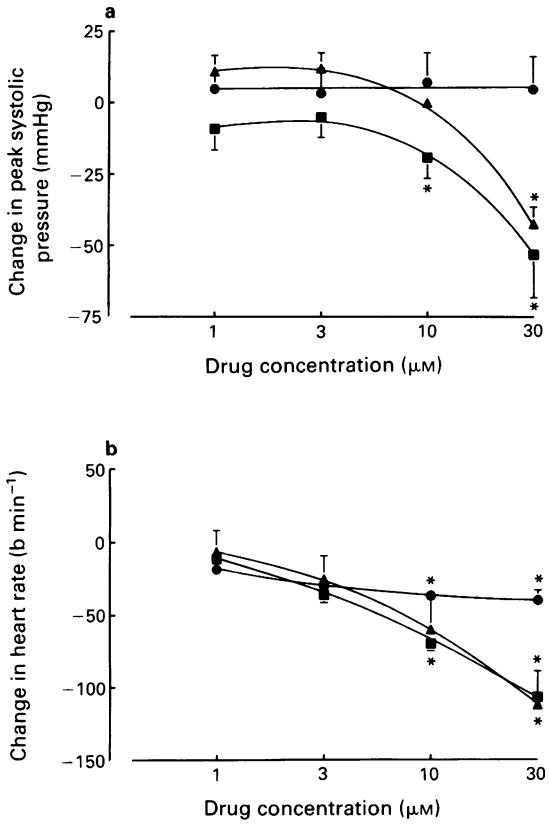

Figure 1 Dose-related effects of U-50,488H on peak systolic ventricular pressure and heart rate in rat isolated perfused hearts: (a) shows changes, from pre-drug values, in peak systolic pressure (mmHg) and (b) heart rate (beats min^{-1}) from pre U-50,488H values. The symbol (●) is for data from control animals treated with saline alone, (■) for U-50,488H treatment, and (▲) for U-50,488H in the presence of naloxone (1.0 μM). Each point is mean with s.e.mean shown by vertical bars, $n = 5$. * $P < 0.05$ for difference from zero change. The pre U-50,488H, or saline, means ranged from 259 ± 11 to 269 ± 12 beats min^{-1} for heart rate and 129 ± 5 to 145 ± 8 mmHg for peak systolic left ventricular pressure.

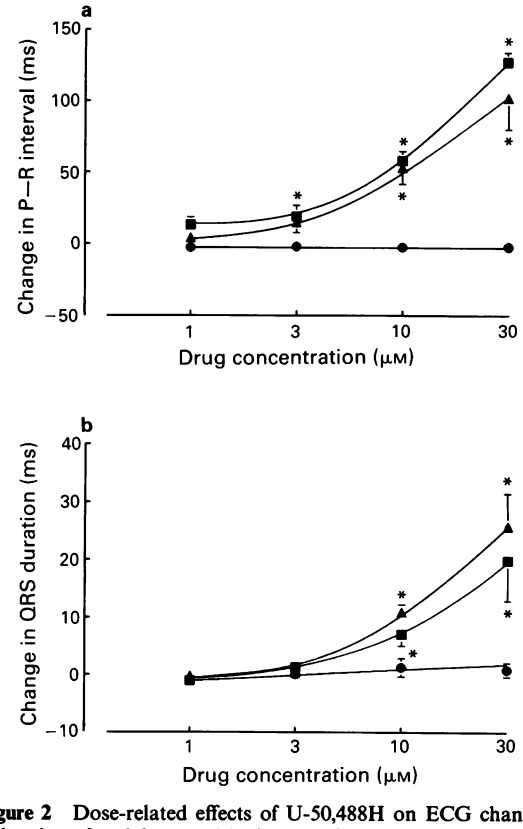

Figure 2 Dose-related effects of U-50,488H on ECG changes in rat isolated perfused hearts: (a) changes, from pre-drug values, in P-R interval (ms) and (b) QRS width (ms). The symbol (●) is for saline control alone, (■) for U-50,488H and (▲) for U-50,488H in the presence of naloxone (1.0 μM). Values are mean with s.e.mean shown by vertical bars, $n = 5$. * $P < 0.05$ for difference from zero change. The pre U-50,488H, or saline, means ranged from 45 ± 2 to 47 ± 3 ms, for P–R, and 33 ± 1 to 35 ± 1 ms for QRS.

with high doses of either MR 2266 or naloxone. The antagonist drugs alone had limited effects; naloxone did not change any of the variables whereas MR 2266 induced slight bradycardia and P–R prolongation (Table 1).

Table 1 The effects of U-50,488H at a dose of 16 μmol kg^{-1} on blood pressure, heart rate and ECG in pentobarbitone-anaesthetized rats in the absence or presence of the opioid antagonists, naloxone and MR 2266 (both at 8 μmol kg^{-1})

Treatment	*Pretreatment*	*Post-treatment*	*Post U-50,488H*	%
		BP (mmHg)		
Saline	132 ± 4	136 ± 6	107 ± 5†	(−20 ± 6)†
Naloxone	137 ± 6	143 ± 5	120 ± 8†	(−16 ± 7)†
MR 2266	136 ± 7	142 ± 9	118 ± 11†	(−18 ± 4)†
		HR (beats min^{-1})		
Saline	365 ± 13	364 ± 6	261 ± 14†	(−25 ± 2)†
Naloxone	405 ± 20	403 ± 25	323 ± 24†	(−20 ± 3)†
MR 2266	389 ± 1	337 ± 20*	271 ± 12†	(−22 ± 3)†
		P–R (ms)		
Saline	49 ± 1	48 ± 1	58 ± 2†	(+18 ± 4)†
Naloxone	47 ± 2	48 ± 2	57 ± 2†	(+20 ± 3)†
MR 2266	48 ± 1*	54 ± 2*	58 ± 2†	(+8 ± 3)†
		QRS (ms)		
Vehicle	29.6 ± 0.7	30.0 ± 0.7	32.8 ± 0.4†	(+10 ± 2)†
Naloxone	28.6 ± 0.4	29.4 ± 0.2	31.8 ± 0.2†	(+8 ± 2)†
MR 2266	30.0 ± 0.8	31.1 ± 0.5	33.8 ± 0.2†	(+9 ± 2)†

Values are mean ± s.e.mean, $n = 5$. BP = mean blood pressure; HR = heart rate. Values in parentheses are the percentage changes between post-treatment and post U-50,488H values. After administration of U-50,488H all values were statistically significantly (†) different ($P < 0.05$) from the pre-U-50,488H, i.e. post-saline, naloxone or MR 2266 treatment values. * $P < 0.05$ for means after treatment with either saline, naloxone or MR 2266 versus pretreatment means.

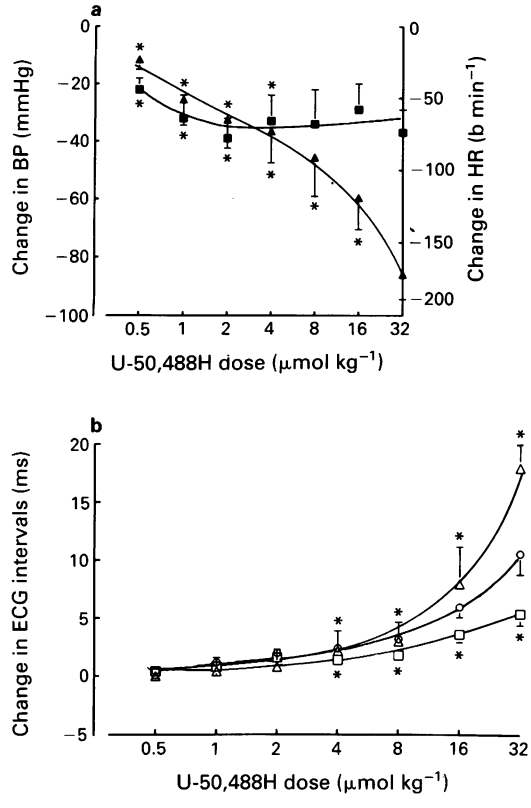

Figure 3 Dose-related effects of U-50,488H on blood pressure, heart rate and the ECG in pentobarbitone-anaesthetized rats: (a) changes, from pre-drug values, in blood pressure (mmHg) and heart rate (beats min^{-1}) while (b) shows the corresponding changes in P–R, QRS and Q–T (ms). The symbol (■) is for blood pressure, (▲) for heart rate, (△) for P–R interval, (□) for QRS and (○) for Q–T. Values are mean with s.e.mean shown by vertical bars, $n = 5$–10. Significant difference from zero change at $^*P < 0.05$. The pretreatment means were 123 ± 8 mmHg for blood pressure, 381 ± 26 for heart rate, 47 ± 1 ms for P–R, 29 ± 1 for QRS and 42 ± 1 for Q–T.

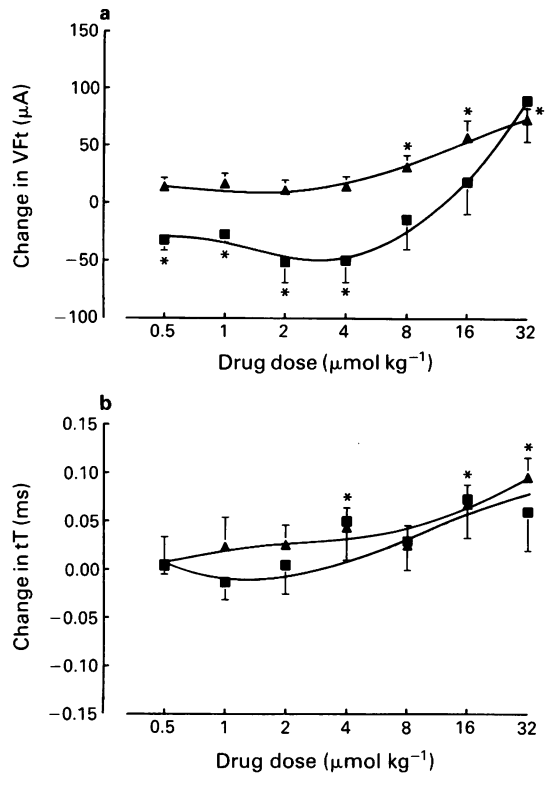

Figure 4 Effects of U-50,488H on ventricular fibrillation threshold (VFt) (a) and threshold pulse width (tT) (b) in pentobarbitone-anaesthetized rats subject to electrical stimulation. The symbol (■) indicates changes from pre-drug values with U-50,488H alone, or in the presence of naloxone pretreatment (▲). Saline control values are not shown but are indicated in the text. Values are mean with s.e.mean shown by vertical bars, $n = 5$–12. $^*P < 0.05$ for difference from zero change. Control (pre-drug) values ranged from 208 ± 15 to $265 \pm 25\,\mu$A for VFt and 53 ± 3 to 54 ± 4 ms for tT.

Figures 4 and 5 summarize the effects of U-50,488H on responses to electrical stimulation in intact rats expressed as changes from values just prior to administration of U-50,488H. Data for saline control rats showed no changes with time over the experimental period. Thus values at the beginning and end of the experimental period in the saline-treated group were 240 ± 25 and $294 \pm 36\,\mu$A for VFt, 0.32 ± 0.04 and 0.27 ± 0.03 ms for tT, 53 ± 3 and 48 ± 4 ms for ERP and 13.9 ± 0.6 and 14.7 ± 0.7 Hz for MFF, respectively.

The dose-dependent changes in VFt produced by U-50,488H (Figure 4) were biphasic in nature. Reductions occurred over the dose range of 0.5–4 μmol kg^{-1} while VFt increased with dose after attaining a minimum value at 4 μmol kg^{-1}. The initial phase of reduced values was greatly attenuated by pretreatment with naloxone. In Figure 4 it can be seen that tT was prolonged in a dose-related manner with only a suggestion of an initial fall and this was not seen after naloxone pretreatment. Similar findings were made with iT. In the absence of naloxone, iT initially fell by $-30 \pm 10\,\mu$A ($P < 0.05$) after a total dose of 4 μmol kg^{-1} and then increased with dose to reach a value of $+79 \pm 34\,\mu$A ($P < 0.05$). With naloxone pretreatment no significant initial fall was seen and iT rose in a monotonic manner with increasing dose.

ERP lengthened dose-dependently at all dose levels (Figure 5a) in a monotonic dose-dependent manner and this was not influenced by naloxone pretreatment. In keeping with the prolongation of ERP, the closely related but different variable, MFF, was dose-dependently reduced. This change was accentuated rather than reduced by pretreatment with 8 μmol kg^{-1} naloxone.

Naloxone, *in vivo*, had no statistically significant effects on electrical stimulation. Thus differences before and after naloxone were $+19 \pm 12\,\mu$A for iT, $+32 \pm 18\,\mu$A for VFt, -0.01 ± 0.03 ms for tT, -0.1 ± 0.8 Hz for MFF and $+2 \pm 4$ ms for ERP. None of these changes was statistically significant.

Discussion

The present study revealed some interesting actions of U-50,488H on rat hearts. These actions occurred at doses and concentrations above those required for κ-agonism and for the most part were not abolished by naloxone. In isolated hearts a naloxone-resistant depression of contractility, rate and the ECG were seen. Similar depression *in vivo* would account at least in part, for reductions in blood pressure and heart rate seen in intact rats.

In both isolated and intact hearts, QRS width and P–R interval were prolonged by U-50,488H in a manner unaffected by naloxone. It is generally accepted that Class I antiarrhythmics, i.e. myocardial sodium channel blockers, can produce increases in QRS width. Prolongation of the P–R interval can be produced by a variety of different drugs including Class I antiarrhythmics.

U-50,488H, at the relatively high doses and concentrations used in this study produced significant actions on responses to electrical stimulation. These included increases in iT, tT and VFt. These responses were characteristic of those produced by blockade of sodium channels in rat heart (Abraham *et al.*, 1989). However, it was noticeable that lower concentrations of U-50,488H, i.e. those most likely to be associated with selective effects on opioid receptors, reduced VFt in a manner that was attenuated by naloxone. The same pattern, but to a less marked extent, was seen with iT and tT. Thus, especially in

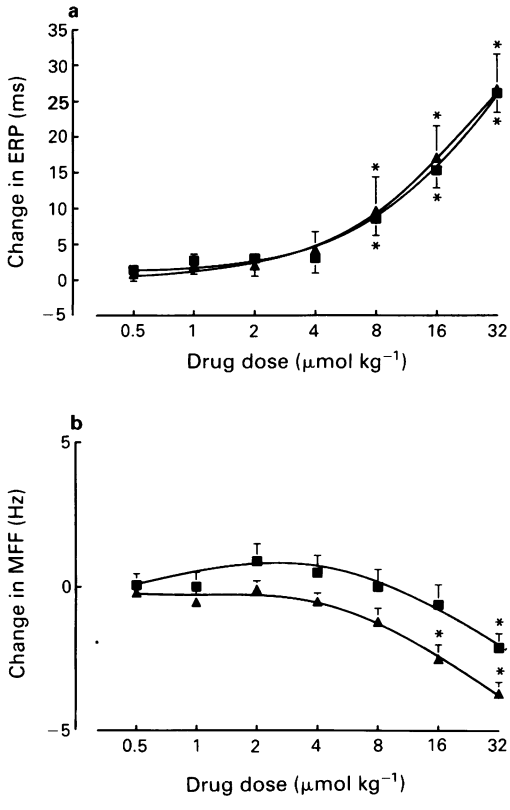

Figure 5 Effects of U-50,488H on effective refractory period (ms) (a) and maximum following frequency (Hz) (b) in pentobarbitone-anaesthetized rats subject to electrical stimulation. The symbol (■) indicates changes from pre-drug values with U-50,488H alone, or in the presence of naloxone pretreatment (▲). Saline control values are not shown but are indicated in the text. Values are mean with s.e.mean shown by vertical bars, $n = 5$–12. * $P < 0.05$ for difference from zero change. Control values ranged from 53 ± 3 to 58 ± 3 ms for ERP and 13.4 ± 0.4 to 15.3 ± 1.0 Hz for MFF.

the case of VFt, U-50,488H appeared to have two actions; a lower dose and possibly arrhythmogenic effect mediated through opioid receptors, and a higher dose and possible anti-arrhythmic effect independent of opioid receptors.

ERP was increased and MFF decreased in a dose-dependent manner by U-50,488H. These are characteristic actions of drugs which block sodium channels and/or prolong action potential duration. U-50,488H prolonged Q–T in the manner typical of a Class Ia antiarrhythmic drug.

In summary the profile of action of U-50,488H, especially at higher doses and concentrations, was consistent with sodium channel blockade. Depression of blood pressure, or contractility, and heart rate, prolongation of P–R and QRS, elevation of thresholds for induction of ventricular fibrillation or capture, are all produced by sodium channel blockade as has been illustrated previously with tetrodotoxin (Abraham *et al.*, 1989). Prolongation of ERP can be expected to occur with Class Ia sodium channel blockers and Class III anti-arrhythmics. It should be noted that for the majority of the measured variables there was a clear dose-response relationship. Even in the case of VFt, where such a dose-response relationship was not so obvious, because of the initial fall, blockade with naloxone clearly revealed the same underlying trend as seen with other variables. In concert with this, preliminary studies (unpublished observations) in rat isolated cardiac cells show that U-50,488H blocks sodium currents in these cells at concentrations found effective in rat isolated hearts.

The relationship between the above findings and potential arrhythmogenic or antiarrhythmic actions of U-50,488H are complex. Thus reductions in VFt seen at lower doses can be interpreted as being arrhythmogenic whereas sodium channel blockade can be either antiarrhythmic or arrhythmogenic in a manner that depends both upon dose and prevailing conditions. Thus U-50,488H may be biphasic in action: arrhythmogenic or pro-arrhythmic, at lower doses, and antiarrhythmic at higher doses. Such actions agree with previous findings in another study in which U-50,488H induced arrhythmias in rat isolated hearts when given in bolus doses (Wong *et al.*, 1990). They also are in agreement with the suggestion that opioid agonists and antagonists have anti-arrhythmic actions independent of opioid receptors (Sarne *et al.*, 1991).

At lower doses the possible arrhythmogenic action of U-50,488H on VFt was blocked by naloxone, indicating an opioid receptor-mediated effect, a finding in agreement with the suggestions of Parratt & Sitsapesan, (1986) and Wong & Lee (1987). Thus the present study helps explain discrepancies as to the effects of opioid agonists and antagonists on arrhythmias (see Sarne *et al.*, 1990).

In a separate study (unpublished observations), we found that U-50,488H, given at a single dose of 8 μmol kg^{-1} had antiarrhythmic actions against arrhythmias induced by occlusion of a coronary artery in anaesthetized rats. These antiarrhythmic actions were not blocked by pretreatment with naloxone. In the present study the same dose, albeit given cumulatively rather than as a single dose, gave incomplete indications of sodium channel blockade. Thus P–R and QRS were both increased by this dose. On the other hand Q–T was increased as was ERP, findings associated with Class Ia actions and/or potassium channel blockade. The 8 μmol kg^{-1} (cumulative) dose was associated with an increased VFT in presence of naloxone but not in its absence, an indication, perhaps, of the presence of sodium blockade masked by an equal but opposite action mediated via κ-agonism. It remains to be tested whether with lower doses, where κ-agonism would be expected to predominate, proarrhythmic actions occur with coronary occlusion in the rat.

In conclusion, the present study provides evidence that U-50,488H, a κ-receptor agonist, can have complex cardiovascular actions. Some of the effects may be mediated via opioid receptors while others, especially at higher doses, are independent of opioid receptors and may involve sodium channel blockade. The exact relationship between the findings in this study and effects on arrhythmias have still to be fully explained.

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