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Electrophysiological effects of melperone on isolated rabbit heart muscles

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1 Electrophysiological effects of melperone on isolated atrial and ventricular muscle preparations of the rabbit were studied by a conventional microelectrode technique.

2 Melperone (3.3 μM) prolonged the action potential duration and effective refractory period of the atrial preparations without affecting the maximum rate of depolarization ($\dot{V}_{max}$). These effects of melperone on action potential duration and effective refractory period were inhibited by a low potassium perfusate (2.7 mM).

3 A high concentration of melperone (16.6 μM) decreased $\dot{V}_{max}$ of atrial preparations. In ventricular muscles, melperone at either concentration decreased $\dot{V}_{max}$, although the increase in action potential duration was greater than in the atrium.

4 Depression of $\dot{V}_{max}$ of ventricular muscles by melperone was found to be augmented by an increase of stimulation frequency and drug concentration.

5 The rate of onset of rate-dependent block of $\dot{V}_{max}$ in ventricle was increased with drug concentration and frequency of stimulation. However, the time constant of recovery from rate-dependent block was almost constant. The kinetics of rate-dependent block of $\dot{V}_{max}$ by melperone were approximately similar to those of quinidine and disopyramide. Consequently it is concluded that melperone possesses class 1a antiarrhythmic activity as well as class 3 activity.

Introduction

Melperone, a neuroleptic butyrophenone, has been shown to possess antiarrhythmic properties *in vitro* (Arlock *et al.*, 1978) and *in vivo* (Petersen, 1978; Refsum, 1981), including clinical efficacy in acute myocardial infarction (Møgelvang *et al.*, 1980). It was reported that in mammalian cardiac muscles, melperone prolonged the action potential duration (APD) and the effective refractory period (ERP) without affecting the maximum rate of depolarization ($\dot{V}_{max}$) and without depressing contractility (Millar & Vaughan Williams, 1982). These effects are typical of antiarrhythmic drugs of class 3, according to the classification of Vaughan Williams (Vaughan Williams, 1970). However, it was found that high concentrations of melperone decreased the maximum rate of depolarization, suggesting that melperone also has class 1 antiarrhythmic activity (Millar & Vaughan Williams, 1982). A recent investigation (Campbell, 1983a) revealed that class 1 antiarrhythmic drugs have different kinetics of depression of $\dot{V}_{max}$ (resting block and rate-dependent block), and rate-dependent block (RDB) is considered to be essential for class 1 antiarrhythmic action. In addition, it was reported that amiodarone, a prototype of class 3 antiarrhythmic drugs, causes a rate-dependent depression of $\dot{V}_{max}$ (Mason *et al.*, 1984). These authors demonstrated that amiodarone depresses the sodium current by selectively depressing the inactivated sodium channels. On the other hand, the kinetics of depression of $\dot{V}_{max}$ by melperone have not yet been studied. Hence, it is necessary to study the kinetics of $\dot{V}_{max}$ depression to delineate the mechanism of class 1 antiarrhythmic action of melperone.

It is important to understand the effects of extracellular K^+ concentration on the electrophysiological properties of antiarrhythmic drugs for clinical administration. For example, the prolongation of

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APD and ERP by disopyramide is accentuated by decreasing the extracellular K^+ concentration (Kojima, 1981). To date, the electrophysiological effects of melperone have been studied only in solutions with normal extracellular K^+ concentration (5.3–5.6 mEq l^{-1}) and the action of melperone in a decreased extracellular K^+ perfusate is unknown.

Thus the purposes of this study were to delineate the effects of melperone on the kinetics of $\dot{V}_{max}$ depression and the influence of changed extracellular K^+ concentration on its class 3 action.

Methods

Albino rabbits of either sex, weighing about 2.5 kg, were anaesthetized with pentobarbitone sodium (30 mg kg^{-1}, i.v.) and given positive-pressure 100% O_2 respiration. The hearts were excised rapidly and placed in cooled modified Tyrode solution (composition, mM: NaCl 137, KCl 2.7, $CaCl_2$ 1.8, $MgCl_2$ 0.47, NaH_2PO_4 0.7, $NaHCO_3$ 11.9, glucose 11.0) saturated with a mixture of 2% CO_2 : 98% O_2. The left atrial and right ventricular muscles were isolated by the method described in a previous paper (Kawai *et al.*, 1981). The left atrial and the right ventricular muscles were cut to suitable sizes (2 × 10 mm). The preparations were fixed in a tissue bath and superfused with modified Tyrode solution warmed to about 35.0°C at a constant rate of about 15 ml min^{-1}. This temperature was maintained within ±0.2°C throughout each experiment.

Rectangular electrical pulses, 2 ms in duration and twice the diastolic threshold in intensity, were delivered through a Teflon-coated bipolar silver wire with a cardiac stimulator, MSE-40 (Nihonkohden) or SEC-2102S (Nihonkohden) as needed. Transmembrane action potentials were obtained with Pyrex capillary microelectrodes filled with 3 M KCl. The electrodes were coupled to silver–silver chloride wires and input to a capacitance-neutralizing amplifier (WPI model 750). Surface electrograms were obtained with a bipolar silver wire electrode and amplified with a differential preamplifier (WPI model DAM-5A or DAM-6A). Monitoring was by means of an oscilloscope (Nihonkohden VC-7 or VC-9) and recordings were made on Polaroid film from the face of a storage oscilloscope (Tektronix 5113) or with an ink-jet paper recorder (Siemens-Elema, Mingograph 800).

For the left atrial and right ventricular muscle preparations, each strip was basically stimulated at a rate of 2 Hz from one side, and the intracellular action potentials were recorded from the other side. The maximum rate of depolarization ($\dot{V}_{max}$), amplitude of the action potential (AP), diastolic resting potential (RP), 20%, 50% and 90% duration of action potentials (APD_{20}, APD_{50} and APD_{90}) and the effective refractory period (ERP) were measured. The ERP of the left atrial and right ventricular muscles were defined as the longest stimulus interval at which a premature stimulus did not elicit a propagated response.

To study the kinetics of the depression of $\dot{V}_{max}$ by melperone, the right ventricular preparations were driven by a series of stimuli at the rate of 2 and 3 Hz, of sufficient duration to achieve a stable level of effect. Rest periods sufficient to ensure full recovery from rate-dependent block (RDB) were interposed between the series of stimuli. The kinetics of this recovery were studied by applying single extra stimuli at varying intervals after the end of a series. The concentrations of melperone used were 3.3, 8.3 and 16.6 μM. Two K^+ concentrations (2.7 and 5.4 mM) of Tyrode solution were used. A single K^+ concentration (2.7 mM) was used for right ventricular preparations to study the kinetics of the depression of $\dot{V}_{max}$.

Statistical analysis was performed by Student's paired *t* test and analysis of variance according to Newman-Keul's multiple comparison. A probability value less than 0.05 was considered significant. The values of the measured parameters are expressed as means ± s.d. Melperone was supplied by AB Ferrosan, Malmö, Sweden.

Results

Atrial myocardium

Effects of melperone on the action potential parameters of left atrial muscles (2 Hz stimulation) were studied at concentrations of 2.7 and 5.4 mM K^+. The results of these experiments are summarized in Table 1. The drug-induced changes in action potential parameters reached a steady state within about 30 min after the start of drug superfusion.

Potassium 5.4 mM Melperone 3.3 μM significantly prolonged APD_{50}, APD_{90} and ERP without changing other parameters. $\dot{V}_{max}$ was slightly increased, although the increase was not significant. At a concentration of 8.3 μM, melperone further prolonged APD_{50}, APD_{90} and ERP, although these changes were accompanied by the significant depression of $\dot{V}_{max}$. Melperone 16.6 μM induced more increase of APD_{50}, APD_{90} and ERP and greater depression of $\dot{V}_{max}$. At this concentration the increase of ERP greatly exceeded that of APD_{50} and APD_{90}. Throughout the experiments, resting potential (RP) and APD_{20} were unchanged.

Potassium 2.7 mM In remarkable contrast to the

Table 1 Electrophysiological effects of melperone on atrial myocardium of the rabbit

K^+ : 5.4 mM *Concentration of melperone*	*ERP* (ms)	APD_{90} (ms)	APD_{50} (ms)	APD_{20} (ms)	$\dot{V}_{max}$ ($V s^{-1}$)	*RP* (mV)	*APA* (mV)
Control (○)	94 ± 7	80 ± 9	45 ± 5	23 ± 3	91 ± 8	−79 ± 3	96 ± 4
3.3 μM	108 ± 14**	93 ± 12**	50 ± 7**	24 ± 3	92 ± 9	−80 ± 3	97 ± 4
8.3 μM	127 ± 12***	106 ± 13***	53 ± 7***	24 ± 3	86 ± 8**	−79 ± 3	97 ± 3
16.6 μM	142 ± 12***	114 ± 11***	54 ± 8***	25 ± 3*	61 ± 7***	−79 ± 2	97 ± 4
K^+ : 2.7 mM							
Concentration of melperone							
Control (○)	100 ± 8	87 ± 7	52 ± 6	29 ± 4	108 ± 11	−92 ± 2	109 ± 3
3.3 μM	102 ± 8	89 ± 8	52 ± 7	29 ± 3	111 ± 13	−93 ± 3	109 ± 4
8.3 μM	116 ± 7**	99 ± 7**	58 ± 8*	29 ± 4	107 ± 12	−94 ± 2	109 ± 4
16.6 μM	129 ± 10***	108 ± 10***	59 ± 8**	30 ± 4	84 ± 11***	−92 ± 3	108 ± 4

Mean results of 6 experiments are shown ±1 s.d. Abbreviations used are described in the text. In this, and subsequent tables, the statistical significance of difference is presented thus: $*P < 0.05$; $**P < 0.01$; $***P < 0.001$.

results with a potassium concentration of 5.4 mM, melperone 3.3 μM hardly prolonged APD_{50}, APD_{90} and ERP at a potassium concentration of 2.7 mM. Other parameters, such as APD_{20}, $\dot{V}_{max}$ and ERP, were also unchanged. Superfusion with 8.3 μM melperone significantly prolonged APD_{50}, APD_{90} and ERP without changing APD_{20}, $\dot{V}_{max}$ and RP. At 16.6 μM melperone, APD_{50}, APD_{90} and ERP were further increased and $\dot{V}_{max}$ reduced significantly. The extent of prolongation of APD_{50}, APD_{90} and ERP by melperone was remarkably small in all cases at a potassium concentration of 2.7 mM compared with that at 5.4 mM. The degree of depression of $\dot{V}_{max}$ by melperone was less at 2.7 mM potassium than at 5.4 mM.

Right ventricle

The results in right ventricular muscles are listed in Table 2.

Potassium 5.4 mM Melperone, 3.3 μM, prolonged APD_{50}, APD_{90} and ERP and decreased $\dot{V}_{max}$ significantly. At higher concentrations of melperone, APD_{50}, APD_{90} and ERP were prolonged and $\dot{V}_{max}$ reduced to a much greater extent than at 3.3 μM.

Table 2 Electrophysiological effects of melperone on ventricular myocardium of rabbit

K^+ : 5.4 mM *Concentration of melperone*	*ERP* (ms)	APD_{90} (ms)	APD_{50} (ms)	APD_{20} (ms)	$\dot{V}_{max}$ ($V s^{-1}$)	*RP* (mV)	*APA* (mV)
Control (○)	127 ± 13	120 ± 12	82 ± 6	51 ± 4	117 ± 9	−86 ± 4	106 ± 5
3.3 μM	157 ± 12***	147 ± 12***	101 ± 5***	53 ± 4	111 ± 9*	−87 ± 4	106 ± 5
8.3 μM	182 ± 13***	158 ± 11***	107 ± 5***	54 ± 4**	100 ± 9**	−86 ± 4	104 ± 5
16.6 μM	200 ± 13***	166 ± 11***	111 ± 4***	56 ± 4**	77 ± 10***	−86 ± 4	105 ± 5
K^+ : 2.7 mM							
Concentration of melperone							
Control (○)	137 ± 11	130 ± 12	91 ± 8	57 ± 5	121 ± 12	−98 ± 4	118 ± 5
3.3 μM	163 ± 13***	152 ± 12***	106 ± 8**	59 ± 6	117 ± 12*	−98 ± 5	118 ± 5
8.3 μM	188 ± 12***	161 ± 11***	111 ± 9***	61 ± 6**	105 ± 10**	−97 ± 5	117 ± 5
16.6 μM	204 ± 13***	168 ± 11***	115 ± 8***	62 ± 6**	80 ± 13***	−97 ± 5	117 ± 6

The mean results of 6 experiments are presented ±1 s.d.

Table 3 Effects of melperone on the kinetics of $\dot{V}_{max}$ of ventricular myocardium of rabbit

Concentration of melperone	*Frequency of stimulation*	*% RB*	*% RDB*	*ROB* (AP^{-1})	*τ off* (s)
8.3 μM		7.2 ± 3.8*			
	2 Hz		15.4 ± 4.5**	−0.131 ± 0.042	3.7 ± 0.6
	3 Hz		26.5 ± 5.1***	−0.092 ± 0.031	3.8 ± 0.7
16.6 μM		13.5 ± 5.1**			
	2 Hz		24.8 ± 6.4***	−0.172 ± 0.065	3.5 ± 0.7
	3 Hz		38.0 ± 9.3***	−0.125 ± 0.053	3.6 ± 0.8

RB, resting block; RDB, rate-dependent block; ROB, rate of onset of block; τ off, rate of recovery from block; AP, action potential.
The mean results of 6 experiments are presented ±1 s.d.

APD_{20} was also significantly prolonged at 8.3 and 16.6 μM melperone.

Potassium 2.7 mM Unlike the effects of melperone in atrial muscles, the effects of melperone on ventricular muscles were little, if at all, influenced by the potassium concentration. That is, melperone 3.3 μM significantly increased APD_{50}, APD_{90} and ERP of ventricular muscles in the perfusate of 2.7 mM potassium, although the extent of prolongation was smaller than in 5.4 mM potassium. It also significantly decreased $\dot{V}_{max}$ at the lowest concentration of 3.3 μM melperone. At concentrations of 8.3 and 16.6 μM, APD_{50}, APD_{90} and ERP were further prolonged and $\dot{V}_{max}$ was depressed more remarkably. APD_{20} was also increased significantly at these concentrations. At each concentration of melperone, the extents of prolongation of APD_{50}, APD_{90} and ERP and depression of $\dot{V}_{max}$ were slightly less at a potassium concentration of 2.7 mM than at 5.4 mM.

The results of the study on the kinetics of depression of $\dot{V}_{max}$ are listed in Table 3 and a representative recording is presented in Figure 1. In the presence of 8.3 μM melperone, $\dot{V}_{max}$ was decreased even in the absence of preceding stimulation (resting block; % RB). After superfusion of melperone, a series of stimuli produced a progressive fall of $\dot{V}_{max}$ to a new plateau level. The magnitude of this fall expressed as a percentage of the initial (resting) value of $\dot{V}_{max}$ was termed the percentage rate-dependent block (% RDB). The rate at which $\dot{V}_{max}$ fell to the new plateau level as a result of melperone superfusion was well-fitted by a single exponential and could thus be expressed in terms of the slope of that exponential (Courtney, 1979). The rate of onset of RDB (ROB) for 8.3 μM melperone was $-0.131 \pm 0.042\,AP^{-1}$ in the series of stimuli at 2 Hz and $-0.092 \pm 0.031\,AP^{-1}$ at 3 Hz. A higher concentration of melperone, 16.6 μM, resulted in ROB of $-0.172 \pm 0.065\,AP^{-1}$ at 2 Hz and ROB of $-0.125 \pm 0.053\,AP^{-1}$ at 3 Hz. The rate of onset of RDB was, therefore, dependent on the concentration of melperone and frequency of stimulation.

On the other hand, the time constant of recovery from RDB (τ off) was 3.7 ± 0.6 s for 8.3 μM melperone at 2 Hz stimulation and it was little affected by drug concentration or frequency of stimulation. Resting block of $\dot{V}_{max}$ by melperone was enhanced dose-dependently.

Discussion

The present results indicate that melperone prolongs both the action potential duration and effective refractory period in a dose-dependent manner without affecting the maximum rate of depolarization ($\dot{V}_{max}$) in rabbit atrial muscles (class 3 action). However, it

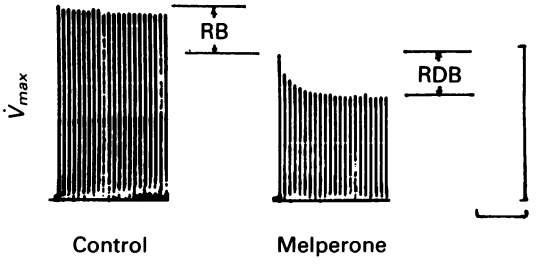

Figure 1 The effect on $\dot{V}_{max}$ of a train of action potentials in previously quiescent right ventricular preparations in control solution (left hand panel) and in the presence of melperone 16.6 μM (right). The interstimulus interval is 500 ms. The spikes represent the $\dot{V}_{max}$ of successive action potentials. There is minor rate-dependent depression of $\dot{V}_{max}$ (RDB) in the control solution and marked depression in the presence of melperone. There is also resting depression of $\dot{V}_{max}$ (resting block, RB) in the presence of melperone. Vertical calibration: $100\,V\,s^{-1}$; horizontal calibration: 5 s.

was also found that high concentrations of melperone decreased the maximum rate of depolarization (class 1 action).

In the present experiments, a prolongation of action potential duration was noted as APD_{50} and APD_{90} in both atrial and ventricular muscles. APD_{20} was not significantly prolonged. Therefore we considered that the class 3 action of melperone was based mainly on its action on phase 3 of repolarization. The total duration of a cardiac action potential depends on a fine balance between slow inward current (I_{si}), slowly activated outward current (I_k or I_{x1}) and background potassium current (I_{bg} or I_{k1}) (Beeler & Reuter, 1977; Trautwein & McDonald, 1978). Inoue *et al.* (1985) recently showed that bethanidine, an analogue of bretylium tosylate, one of the class 3 antiarrhythmic drugs, prolonged the plateau phase (phase 2) of the action potential possibly by increasing the slow inward current.

However, in our present experiments, the action potential duration was prolonged mainly by the lengthening of the phase 3 repolarization (that is, APD_{50} and APD_{90}), not by the prolongation of the plateau phase (APD_{20}). According to Isenberg *et al.* (1982), calcium currents of ventricular myocytes are fast and inactivated rapidly. Therefore, the class 3 action of melperone might be attributed to the effect on the outward currents, such as I_k or I_{bg}.

Final conclusions concerning the ionic mechanism of the class 3 action of melperone must wait until voltage clamp analysis of the action of melperone is performed.

The relationship between extracellular potassium concentration and the class 3 action of antiarrhythmics has not been studied extensively, although it is of special clinical concern. It is reported that bretylium tosylate prolonged the action potential duration of rabbit ventricular muscles considerably, especially when the extracellular potassium concentration was low (Bigger *et al.*, 1971; de Azevedo *et al.*, 1974). Cobbe & Manley (1985) found that the class 3 action of sotalol was preserved at high potassium concentrations but they did not investigate the effect of low potassium concentrations. In addition to the original class 3 antiarrhythmics, the effects of extracellular potassium concentration on the class 3 action of class 1 antiarrhythmics have been reported. Kojima (1981) found that prolongation of the action potential by disopyramide in guinea-pig papillary muscles was favoured by a low potassium perfusate. On the other hand, it has been reported that the prolongation of the action potential by procainamide is favoured by a high potassium perfusate (Sada *et al.*, 1979). We have confirmed that the class 3 action of melperone is favoured by increasing the extracellular potassium concentration as with procainamide, and in contrast to bretylium and disopyramide where low potassium has this effect.

Our experiments on the kinetics of $\dot{V}_{max}$ depression by high concentrations of melperone showed that melperone could produce both resting and rate-dependent block of $\dot{V}_{max}$. This action was enhanced dose-dependently; that is, a higher concentration of melperone produced a faster onset and greater degree of rate-dependent block. Although the rate of onset of block was dependent on the stimulation rate, the rate of recovery from block was not. All these results were considered to be compatible with the modulated receptor theory (Hondeghem & Katzung, 1984). Various kinetics of rate-dependent depression of $\dot{V}_{max}$ by class 1 antiarrhythmic drugs have been reported recently (Campbell, 1983b). For example, the rates of onset of rate-dependent block for disopyramide, quinidine and procainamide are reported to be $0.113 \pm 0.007\,AP^{-1}$, $0.068 \pm 0.005\,AP^{-1}$ and $0.055 \pm 0.003\,AP^{-1}$, respectively at a stimulation frequency of 3.3 Hz. Our results have shown that melperone resembles disopyramide in its kinetics of onset of rate-dependent block.

In the present study, melperone showed relatively faster kinetics of recovery from rate-dependent block (τ off: 3.7 ± 0.6 s). The time constant of recovery was near to that of quinidine (τ off: 4.7 s), rather than disopyramide (τ off: 12.2 s). It is reported that the rates of onset of and recovery from rate-dependent block correlate well with molecular weight of the drug (Campbell, 1983a). As for the onset of block, melperone (mol. wt. 301) showed approximately similar kinetics to that of disopyramide (mol. wt. 339). On the other hand, the recovery kinetics of melperone were rather nearer to those of quinidine (mol. wt. 324). This discrepancy between molecular weight and kinetics of recovery from rate-dependent block might be explained by the condition of ionic charge or stereospecificity of each drug (Campbell, 1983a).

Melperone was proposed as one of the promising class 3 antiarrhythmic drugs by Vaughan Williams (Millar & Vaughan Williams, 1982). The reported serum concentrations of melperone ranged from 0.2 μM to 2.0 μM during clinical administration (Refsum *et al.*, 1978). Therefore the lowest concentration used in our present experiments was comparable to the clinically administered dose.

In the present experiments it was shown that melperone possesses unique class 1a action as well as class 3 action. The effects of antiarrhythmic drugs *in vivo* are affected by their actions on the autonomic tone, the inotropic state of the heart, and the state of the central nervous system, as well as their direct antiarrhythmic actions. The postsynaptic α-adrenoceptor antagonism (Petersen, 1981), the positive inotropism (Smiseth *et al.*, 1981; Platou *et al.*,

1982) and the bradycardic effect of melperone (Millar & Vaughan Williams, 1982) might favourably affect the direct antiarrhythmic actions of melperone, studied in our experiments.

In conclusion, melperone possesses class 3 and class 1a antiarrhythmic effects and it is worth performing extensive animal experiments *in vivo* and clinical antiarrhythmic trials with this drug.

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