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A protective effect of sulphinpyrazone against coronary occlusion-induced shortening of myocardial refractory periods in the rat

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1 The hearts of anaesthetized, artificially ventilated rats were exposed, and the left coronary artery occluded. The diastolic threshold voltage for stimulation (DTV), the duration of the bipolar electrogram (DBE) and the functional refractory period (FRP) of the ischaemic area were measured at minute intervals for an hour after occlusion.

2 Coronary occlusion caused a rise in DTV, a prolongation of the DBE and a biphasic change in the FRP, with an initial prolongation phase (1–4 min) followed by a decline to below pre-occlusion values (5–15 min).

3 Episodes of ventricular tachyarrhythmia (VT) were most frequent during the period 5–15 min after the onset of occlusion of the coronary artery. This coincided with the period when FRP was minimal and the difference between DBE and FRP was maximal.

4 Pretreatment of rats with sulphinpyrazone (2.5–40 mg kg^{-1}) or indomethacin (5–20 mg kg^{-1}) protected against the episodes of coronary occlusion-induced VT and against the associated decline in FRP of the ischaemic muscle. Sulphinpyrazone was more effective than indomethacin in this respect and a combination of the two drugs was approximately as effective as sulphinpyrazone alone.

5 It was concluded that sulphinpyrazone protects rats against coronary occlusion-induced episodes of VT by reducing the risk of ventricular action potential re-entry. This effect is probably due to protection against the ischaemia-induced shortening of the myocardial FRP.

Introduction

In a large multi-centre controlled clinical trial (Sherry, 1978; 1980; 1982), daily oral administration of 4 doses of sulphinpyrazone for a year reduced the incidence of what was judged to be sudden cardiac death among those patients who survived an acute myocardial infarction for long enough to be discharged from hospital. By definition, sudden cardiac death is due to a disturbance of cardiac rhythm. When it occurs in a person with ischaemic heart disease it is usually considered to be due to some form of ventricular tachyarrhythmia (VT). The pharmacological mechanism whereby sulphinpyrazone protects the ischaemic myocardium against such disturbances of rhythm, however, remains uncertain. The drug possesses little or no anti-arrhythmic action of a conventional type when tested on healthy myocardium at doses or concentrations comparable with those that are used in clinical practice (Benditt *et al.*, 1980; Kristiansen *et al.*, 1982; Wyse, 1985). Nevertheless, sulphinpyrazone protects the heart against disturbances of cardiac rhythm after experimental coronary artery occlusion. This has been shown in the dog (Povalski *et al.*, 1980; Moschos *et al.*, 1981), in the cat (Kelliher *et al.*, 1980), and in the rat (Brunner *et al.*, 1980; Lepran *et al.*, 1981), although the drug was reported to be inactive in the pig (Staubli *et al.*, 1984). Sulphinpyrazone has also been shown to protect animal hearts against some but not all of the biochemical and histological consequences of coronary artery occlusion (Kelliher *et al.*, 1980; Povalski *et al.*, 1980; Bolli *et al.*, 1981; Innes & Wiseman, 1981; Moschos *et al.*, 1981; Karmazyn, 1984). It was of interest, therefore, to examine the effects of sulphinpyrazone on the electrical changes that occur within ischaemic myocardium.

Methods

Male albino rats of the Sprague-Dawley strain weighing 350–460 g were anaesthetized by subcutaneous injection of a 25% solution of urethane and maintained at a rectal temperature of 36 ± 1.5°C on a

warmed operating table. A lead 2 electrocardiogram was recorded via subcutaneous needle electrodes and displayed on a dual channel scroll-type storage oscilloscope (Cardiostore SEM 431, made by SE Laboratories). The electrocardiogram was also recorded on a magnetic tape cassette recorder (Medilog series 4–24, made by Oxford Medical). These tapes were replayed at the end of the experiment via a DDA2 analysis unit made by the same company. Freshly prepared solutions of the sodium salts of sulphinpyrazone or indomethacin were administered via the right jugular vein. Intermittent positive pressure ventilation was applied at a rate of 60 strokes per minute via a tracheal cannula. Tidal volumes were adjusted to maintain arterial P_{CO_2} within the normal range (35–45 mmHg).

A left parasternal thoracotomy was performed, the ribs retracted and the pericardial sac opened. The temperature of the epicardial surface was maintained at 34 ± 3°C by means of radiant heat from a lamp. A braided silk suture, size 6/0, with round bodied curved needle attached (Type W593 Mersilk, made by Ethicon) was placed beneath the left coronary artery as described in detail previously (Northover, 1985). The artery was able to be occluded for any desired length of time by tightening this ligature through a snare made from a short length of thick-walled plastic tubing.

Four wire electrodes (diameter 150 μm) of the type described by Kaplinsky *et al.* (1980) were inserted into the myocardium via the lumen of 26 gauge hypodermic needles. Their hooked ends were impaled on the endocardial surface of the left ventricular free wall in a region expected to become cyanosed and to show systolic bulging after occlusion of the left coronary artery. The wires were insulated except at their ends and were separated from each other by approximately 2 mm. Care was taken to avoid applying traction to the wire electrodes which might have injured the myocardium. Unfiltered bipolar electrograms were recorded by connecting one pair of wires via a differential d.c. amplifier to both an oscilloscope (Type 3131, made by Dynamic Electronics) and a heated stylus recorder with a paper speed of 100 mm s^{-1} (Type M2, made by Devices). The duration of the bipolar electrogram (DBE) was measured from the beginning of the first deflection to the end of the last deflection. Thus, it represents the entire duration of electrical systole of all muscle fibres situated between the recording electrodes. Measured in this way both action potential duration and the apparent speed of action potential conduction contribute to the observed DBE. The second pair of wire electrodes was used for pacing the ventricles at 7 Hz with 1 ms pulses adjusted at 1 min intervals throughout the experiment to twice the prevailing diastolic threshold voltage (DTV). Refractory periods were measured using paired stimuli of progressively wider spacing. The shortest interval between members of a pair of stimuli both of which elicited an electrogram response was taken as the effective refractory period (ERP). The interval between the two electrogram responses so elicited was taken as the functional refractory period (FRP). Where the second stimulus of a pair elicited multiple electrogram responses the FRP was taken as the interval between the more closely spaced of the first 2

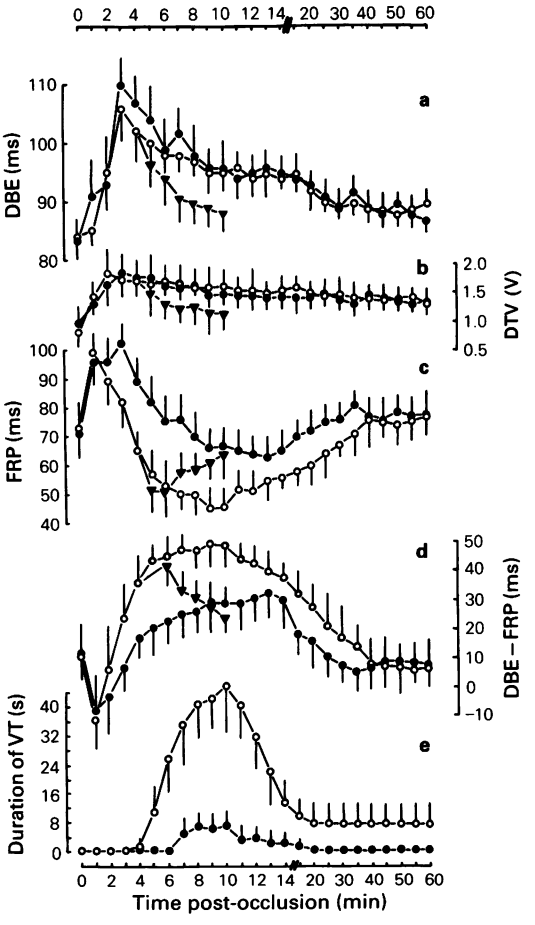

Figure 1 Coronary artery occlusion was at time zero. Control rats were pretreated with saline and subjected (n = 10–15) to permanent occlusion (○) or reperfused (n = 12) after 4 min of occlusion (▼). Ten paced and 12 unpaced rats (●) were subjected to permanent occlusion 6 min after pretreatment with sulphinpyrazone (40 mg kg^{-1}). In paced hearts the duration of the bipolar electrogram (DBE, a), the diastolic threshold for stimulation (DTV, b), and the functional refractory period (FRP, c) were recorded. In the unpaced hearts (e) the total duration of the episodes of ventricular tachyarrhythmia (VT) was recorded during each minute after coronary occlusion. Vertical bars represent s.e.mean.

responses. Animals which developed fatal arrhythmias were not resuscitated.

Results

Unpaced hearts

Rats subjected to permanent coronary artery occlusion, but not electrically stimulated, showed numerous episodes of VT in their electrocardiograms. These episodes were usually short, self-limiting and characterized by varying QRS shape. For reasons described previously (Northover, 1985), no attempt was made to subdivide or classify these episodes into ventricular tachycardia, ventricular flutter or ventricular fibrillation. Instead, the total time spent in these combined forms of VT was noted during each minute of the experiment. Paroxysms of VT usually began after a delay of between 4 and 7 min and continued thereafter for another 6–12 min, as shown in Figure 1. Animals were monitored for 60 min from the start of occlusion, at the end of which time the survivors were killed and the hearts examined under a dissecting microscope to verify correct placement of the coronary ligature.

Rats subjected to 8 min of coronary artery occlusion followed by reperfusion, but without electrical stimulation, developed a particularly severe form of VT (Table 1), usually starting within 15 s of the release of the snare. In 78% of the non-drug treated animals, reperfusion evoked permanent and fatal VT. In contrast, reperfusion after only 4 min of occlusion elicited VT in only one of the 12 animals tested, and that was self-limiting, thus permitting a more detailed electrophysiological study (see below).

Paced hearts

While hearts were being paced, but during periods when the left coronary artery was allowed to remain patent, values of DTV, DBE, ERP and FRP recorded at minute intervals for up to an hour showed no statistically significant change. Within 1–2 min of permanent coronary occlusion, however, the DBE lengthened, with peak values being reached within the first 3 min, followed by a slow and incomplete recovery towards pre-occlusion values, as shown in Figure 1. The DTV increased after occlusion, reaching a maximum after about 3 min, followed by a slow and incomplete restoration towards pre-occlusion values, as shown in Figure 1. Pacing stimuli were adjusted throughout the experiment to a value twice the DTV. Measured in this way both ERP and FRP lengthened within the first minute after occlusion. Indeed, at the end of the first minute of occlusion the FRP was longer than the DBE, indicating the existence of post-repolarisation refractoriness. During the period 4–15 min after the start of occlusion there was a swift decline of FRP to below the pre-occlusion value, followed thereafter by a restoration of normality (Figure 1).

Electrograms recorded from the ischaemic area

Table 1 Protective effect of sulphinpyrazone and indomethacin on the ischaemic myocardium

			Paced electrograms after 10 min occlusion			*Duration of spontaneous VT* (s)	
Drug	*Dose* (mg kg^{-1})	*Time*† (min)	*DBE* (ms)	*FRP* (ms)	*DBE − FRP* (ms)	*Permanent occlusion (0–30 min)*	*Reperfusion*‡ *(8–30 min)*
Control	—	—	95 ± 2*	46 ± 6*	49 ± 7*	325 ± 19§	1257 ± 208§
Sulphinpyrazone	40	−6	96 ± 2	67 ± 4*	29 ± 5*	51 ± 22*	28 ± 15*
Sulphinpyrazone	10	−6	95 ± 3	60 ± 5*	35 ± 3*	87 ± 15*	96 ± 30*
Sulphinpyrazone	2.5	−6	97 ± 2	58 ± 7	39 ± 6	102 ± 26*	130 ± 71*
Sulphinpyrazone	40	−60	95 ± 2	59 ± 8	36 ± 8	108 ± 18*	155 ± 54*
Sulphinpyrazone	40	+1	96 ± 3	56 ± 5	40 ± 2	120 ± 28*	262 ± 89*
Indomethacin	20	−6	98 ± 4	54 ± 6	44 ± 5	117 ± 22*	308 ± 95*
Indomethacin	5	−6	97 ± 3	50 ± 7	47 ± 4	182 ± 31*	723 ± 108*
Indomethacin	1.25	−6	94 ± 2	45 ± 8	49 ± 6	300 ± 57	1094 ± 220
Indomethacin plus sulphinpyrazone	5 40	−6	95 ± 2	69 ± 5*	26 ± 7*	21 ± 11*	63 ± 10*

†Drugs administered before (negative sign) or after (positive sign) the start of occlusion, which was taken as time zero. ‡Reperfusion began 8 min after occlusion. §There were 15 permanently occluded control hearts and 19 reperfused control hearts, with between 7 and 12 animals in each drug-treatment group. Duration of bipolar electrogram (DBE), functional infractory period (FRP), DBE − FRP and ventricular tachyarrhythmia (VT) quoted as mean ± s.e. *$P<0.05$, significantly different from control. *There were 10 paced animals in the control group and each of the treatment groups.

during ventricular pacing showed a progressive decline in voltage amplitude during the first 15 min of ischaemia and thereafter tended to increase again slowly, but in only a minority of animals was the pre-occlusion value re-attained. No such changes occurred in the absence of coronary occlusion. During paired stimulation the changes in electrogram amplitude usually were more marked with the response to a second stimulus of a closely spaced pair than to the corresponding first stimulus. The contrast in electrogram amplitude between first and second responses became more marked as the FRP progressively shortened during ischaemia.

Reperfusion of the myocardium after 4 min of occlusion caused both the DBE and the DTV to return to their pre-occlusion values over the course of the next few minutes, as shown in Figure 1. Immediately after reperfusion, however, the FRP shortened before increasing again towards its pre-occlusion value (Figure 1). Similar experiments in rats subjected to 8 min of occlusion prior to reperfusion were not practicable due to the rapid onset of permanent VT (Northover, 1985).

Effects of sulphinpyrazone

Intravenous administration of sulphinpyrazone shortly before permanent coronary artery ligation protected the unpaced rat heart against episodes of VT (Table 1). In a similar range of doses the drug also reduced the delayed phase of shortening of the FRP in paced hearts subjected to permanent coronary artery occlusion (Figure 1 and Table 1). In contrast, the prolongation of the DBE, the rise in the DTV, and the initial phase of lengthening of the FRP were not significantly altered by the drug (Figure 1). The drug was highly effective also in preventing the widening of the difference between DBE and FRP that was produced between 4 and 20 min after coronary artery occlusion (Figure 1). The protective effect of sulphinpyrazone was dose-related, almost immediate in onset, but rather brief, as shown in Table 1. The drug also exerted some protective effect on the ischaemic area even when administered after the start of permanent coronary occlusion, suggesting that pharmacologically significant amounts of the drug may enter an already ischaemic area, presumably via collateral channels.

Intravenous administration of sulphinpyrazone before an 8 min period of coronary occlusion prevented the VT which followed almost immediately upon reperfusion in most of the non-drug treated animals, as shown in Table 1. At a dose of 20 mg kg^{-1} the drug was also effective in preventing the brief further decline in FRP seen following reperfusion after a 4 min period of occlusion (data not shown). In the absence of coronary occlusion sulphinpyrazone failed to produce a significant change in any of the measured electrical parameters, even in doses of up to 80 mg kg^{-1}. Higher doses were not tested.

A comparison of the effects of indomethacin and sulphinpyrazone was then undertaken. Intravenous administration of indomethacin (5–20 mg kg^{-1}) prior to permanent coronary occlusion protected unpaced rat hearts against episodes of VT (Table 1). Indomethacin also reduced the shortening of FRP which occurred in paced hearts subjected to permanent coronary occlusion (Table 1). Compared with sulphinpyrazone, however, indomethacin was only weakly protective in maximal tolerated doses (20 mg kg^{-1}). A combination of sulphinpyrazone (40 mg kg^{-1}) and indomethacin (5 mg kg^{-1}) exerted a protective effect which was approximately equal to that exerted by a dose of 40 mg kg^{-1} of sulphinpyrazone alone (Table 1).

Discussion

Several groups of workers have confirmed the early observation of Brooks *et al.* (1960) that 5 to 15 min after the onset of experimental coronary artery occlusion the myocardial action potential in the ischaemic area shortens and the speed of action potential conduction slows. Most studies have used either the dog or the pig, the subject having been reviewed from the point of view of these two species by several investigators (Elharrar & Zipes, 1977; Lazzara *et al.*, 1978; Janse, 1982; Horacek *et al.*, 1984). By comparison, the early ischaemia-induced electrical changes in the rat myocardium have been studied only rarely, (Budden *et al.*, 1981; Mertz & Kaplan, 1982). The limited information available, however, suggests that the rat heart resembles that of the other two species in its response to ischaemia.

Abbreviation of action potential duration caused by acute ischaemia tends to shorten the DBE. However, in most studies, any such effect on DBE has been more than fully offset by concomitant slowing of action potential conduction, at least in the dog (Boineau & Cox, 1973; Scherlag *et al.*, 1974; Hope *et al.*, 1977; Kaplinsky *et al.*, 1978; 1979; 1980; Levine *et al.*, 1978; Ruffy *et al.*, 1979; Russell *et al.*, 1979; Stewart *et al.*, 1980). In the present experiments ischaemia lengthened the DBE, despite the reduced action potential duration which is known to occur in the rat heart under these circumstances (Inoue *et al.*, 1984). This indicates that ischaemia slows action potential conduction in the rat heart as it does in the dog. Unfortunately, attempts to measure rates of action potential conduction within the ischaemic area of the rat heart in the present experiments yielded inconsistent results. This was probably due to the short distances involved.

Refractory periods have been reported to undergo various changes during myocardial ischaemia, although shortening has been the most common finding (Levites *et al.*, 1975; Downar *et al.*, 1977; Bastford *et al.*, 1978; Levine *et al.*, 1978; Bissett *et al.*, 1979; Levites & Anderson, 1979; Stewart *et al.*, 1980). Failure of the refractory periods to shorten in the face of the universally observed shortening of action potential duration has usually been attributed by previous workers to a state of post-repolarisation refractoriness (Lazzara *et al.*, 1978; Bissett *et al.*, 1979). Indeed, some post-repolarisation refractoriness was present during the first 3 min of ischaemia in the present experiments. Comparisons of the present findings with those of previous workers are complicated by the varied stimulation conditions employed. For example, Elharrar *et al.* (1977) showed that when canine myocardial ischaemia had persisted for 20–30 min measured refractory periods shortened if the electrical pacing stimuli used were of twice the prevailing DTV. Using stimuli kept at twice the pre-occlusion value of DTV, on the other hand, yielded a prolongation of refractory periods. In the present study pacing stimuli were re-adjusted throughout the experiment to twice the prevailing DTV, and the results obtained confirm those of Elharrar *et al.* (1977) made under comparable circumstances. In contrast to the experiments of Elharrar *et al.* (1977), however, refractory periods were measured in the present experiments at minute intervals from the start of coronary occlusion. Had an early lengthening phase of refractory periods occurred in the experiments of Elharrar *et al.* (1977), as was the case in the present experiments, it would have been missed by the previous workers.

The FRP of the non-ischaemic myocardium in the present experiments was only slightly shorter than the DBE (Figure 1). The more the DBE exceeds the FRP, however, the earlier in the course of one electrogram response is a second able to be elicited by a suitably timed early stimulus and the greater is the opportunity for the second action potential of such a closely spaced pair to encounter muscle fibres within the recording zone still refractory from the first. Under these circumstances the second action potential will conduct only in certain directions. Such undirectional block of conduction is a known prerequisite for action potential re-entry. It is probably not a coincidence, therefore, that ischaemia-induced episodes of VT were most prevalent in the present experiments during the time of the greatest disparity between DBE and FRP (Figure 1). Previous workers have noted that during early myocardial ischaemia the period of maximal VT severity coincided either with the period of greatest prolongation of the DBE (Kaplinsky *et al.*, 1978; 1979; 1980), or with the period of greatest shortening of refractory periods (Bissett *et al.*, 1979). In the present experiments the period of the most intense VT coincided with the period of the greatest shortening of the FRP, but was beyond the time of maximal prolongation of the DBE (Figure 1). In this connection it is probably significant that Janse (1982) found that re-entry ventricular activity occurred only when the bipolar electrogram from an ischaemic area was able to be interrupted by an action potential arising elsewhere, indicating that the refractory period of the ischaemic area at that time was shorter than the DBE. Formal proof of the occurrence of re-entry of ventricular action potentials in an ischaemic heart has been obtained so far probably only in the pig (Janse *et al.*, 1980; Janse, 1982), and required mapping of the re-entry path adopted. One may deduce, however that an opportunity for re-entry exists when the DBE exceeds the FRP, and that the greater the disparity between them the greater is the risk. In the rat this occurs about 10 min after the onset of coronary occlusion, and coincides with the period of most intense VT activity.

Sulphinpyrazone was found to protect the rat heart against episodes of VT during permanent coronary occlusion in the present experiments. This confirms several previous findings (see Introduction). A new observation from the present experiments was that sulphinprayzone also protects against ischaemia-induced shortening of refractory periods, whereas the other measured electrical parameters were unaltered by the drug. The doses of sulphinpyrazone needed to produce these two protective effects were similar, as were the durations of their respective actions. It seems reasonable to conclude, therefore, that by preventing the ischaemia-induced shortening of refractory periods the drug was able to prevent ventricular action potential re-entry and thereby prevent episodes of VT in the unpaced hearts.

The pharmacological mechanisms responsible for the protective action of sulphinpyrazone against ischaemia-induced shortening of the FRP in the rat heart is unknown. The drug has a well-documented inhibitory action on platelet aggregation and secretion (Pedersen & Fitzgerald, 1985). The drug also improves coronary collateral blood flow during experimental coronary occlusion in the dog (Davenport *et al.*, 1981), but the extent to which this depends upon inhibition of platelet function is unknown. Although the rat heart possesses an extensive system of coronary collaterals (Maclean *et al.*, 1978), their functional significance and relationship to platelet function are unknown. Nevertheless, had sulphinpyrazone exerted its protective action against ischaemia-induced shortening of refractory periods mainly by promoting collateral blood flow one would have expected the drug to blunt all of the electrical disturbances created by the coronary occlusion. Since only the refractory periods were influenced by the drug it seems unlikely that improved myocardial blood flow was the major factor in the protection. However, under some circumstances, sul-

phinpyrazone does seem to exert its protective action on the ischaemic myocardium by improving blood flow. Thus, Karmazyn *et al.* (1981) showed that the drug prevents coronary artery constriction in response to injurious agents, and this was attributed to prevention of entry of calcium ions into smooth muscle cells in the vessel wall. In this connection it may be relevant that certain endogenous products of arachidonic acid oxidation have marked effects upon coronary vascular diameter. Coker (1982) has reviewed the evidence that during myocardial ischaemia there is a balance between a vasconstrictive effect from thromboxane A_2 and a vasodilatation from concomitantly formed prostacyclin. If this is correct, a drug which selectively inhibited the formation (or action) of thromboxane A_2 would be expected to protect against the arrhythmias and other consequences of ischaemia. A drug which was equally inhibitory of both thromboxane A_2 synthesis and prostacyclin synthesis, on the other hand, would be expetced to be less protective. Coker (1982) has reviewed the evidence that the weakly protective effect of indomethacin, for example, can be accounted for in this way. In contrast, Livio *et al.* (1980) found that sulphinpyrazone inhibited thromboxane A_2 synthesis without inhibiting prostacyclin synthesis in the rat. This sort of explanation would certainly be compatible with the greater protective effect of sulphinpyrazone than that of indomethacin in the present experiments (Table 1). It is incompatible, however, with the fact that a combination of indomethacin and sulphinpyrazone was no less effective than that of sulphinpyrazone alone in the present experiments (Table 1).

It seems necessary, therefore, to account for the anti-arrhythmic action of sulphinpyrazone in the present experiments by a direct action of the drug upon the injured cardiac myocytes. Karmazyn (1984) has shown such a protective action in the rat heart and Iansmith *et al.* (1979) showed that sulphinpyrazone renders the isolated myocardium less sensitive to the deleterious effects of an unphysiologically low pH. Myocardial pH certainly declines during coronary occlusion (Hirsch *et al.*, 1982), so this mechanism may be relevant to the present experiments.

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