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Stereospecific antiarrhythmic effect of opioid receptor antagonists in myocardial ischaemia

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The effects of the stereoisomers of two different antagonists at opioid receptors were examined on the ventricular arrhythmias that result from acute coronary artery ligation in anaesthetized male rats. (−)-Mr 1452 (but not the (+)-isomer, Mr 1453) reduced, in a dose-dependent manner, the number of ventricular ectopic beats and the incidence or duration of both ventricular tachycardia and fibrillation. (−)-WIN 44,441-3 (but not its (+)-isomer, WIN 44,441-2) had a similar protective effect in ischaemia. These results suggest that antagonism of the effects of endogenous opioid peptides at specific receptors results in reduced severity of arrhythmias in myocardial ischaemia.

Introduction We have previously shown that both naloxone (Fagbemi *et al.*, 1982) and meptazinol (Fagbemi *et al.*, 1983) reduce the incidence and severity of ventricular arrhythmias resulting from acute coronary artery occlusion in both anaesthetized and conscious rats. For example, in the conscious rat model, naloxone increased survival (assessed at 16 h after occlusion) from 27%, in the controls, to 73%. This significantly improved survival was presumably mainly due to an antiarrhythmic effect of the compound since it reduced the incidence of ventricular fibrillation (VF) from 88% to 18% and of ventricular tachycardia (VT) from 92% to 27%. Indeed, 36% of rats pretreated with naloxone had no arrhythmias at all after coronary artery occlusion; in contrast, all of the controls developed VF, VT and/or multiple ventricular ectopic beats.

One of the problems with the above studies was the possibility that the protection observed might have been unrelated to antagonism at specific opioid receptors. For example, the action potential duration, recorded from papillary muscles of rats pretreated with meptazinol, was greatly prolonged and the maximum rate of depolarization was reduced in sheep Purkinje fibres superfused with the drug. These effects might not be related to actions at receptor level. One way to determine whether opioid receptors are involved would be to use stereoisomers and we now describe such studies with drugs acting at opioid receptors, principally of the μ- and κ-types.

Methods The experiments were all performed on male Sprague-Dawley rats weighing between 200 and 300 g. The rats were anaesthetized with pentobarbitone sodium (6 mg 100 g^{-1}, i.p.) and catheters were placed in a carotid artery (for pressure measurement) and in a femoral vein (for drug injection). The electrocardiogram was recorded from standard limb leads and the rats were subjected to coronary artery occlusion as described in detail by Clark *et al.* (1980). Early post-occlusion arrhythmias were assessed by counting the number of ventricular ectopic beats (VEBs) over the initial 30 min post-occlusion period and by measuring the incidence and duration (in seconds) of ventricular tachycardia (VT) and ventricular fibrillation (VF) as described by Clark *et al.* (1980).

The stereoisomers (−)-Mr 1452 and (+)-Mr 1453 (kindly donated by Dr H. Merz of Boehringer, Ingelheim) and (+)-WIN-44,441-2 and (−)-WIN-44,441-3 (supplied by Dr E. Soria of Sterling Winthrop, U.S.A.), were dissolved in slightly alkaline normal saline and administered intravenously 15 min before coronary artery occlusion.

Results These are summarized in Table 1. As far as the WIN compounds were concerned, a significant beneficial effect was obtained with the (−)-isomer; no VF occurred and the number of VEBs was markedly reduced. No such significant effect was observed with the (+)-isomer, although there was a trend towards an antiarrhythmic effect. In the Mr series, 1452 inhibited the arrhythmias in a dose-dependent manner, with complete abolition of VF at the highest dose used. The (+)-isomer Mr 1453 was much less active, with no significant reduction in VEBs, VT or VF at any dose.

Discussion The present results can be explained on the basis that blockade of opioid receptors, perhaps in the myocardium itself, decreases the severity of ischaemic arrhythmias by reducing the effects of endogenous opiates released as a consequence of the stress of coronary occlusion. On the basis of the

Table 1 Effect of the stereoisomers (−)-Mr 1452 and (+)-Mr 1453 and (−)-WIN 44,441-3 and (+)-WIN 44,441-2 on the incidence and severity of ventricular arrhythmias resulting from acute coronary artery occlusion in anaesthetized rats

	n	*VEBs*	*Duration (in s) and % incidence of* *VT*	*VF*
Controls	16	1011 ± 280	42 ± 14 (94)	21 ± 12 (56)
WIN 44,441-3 (3 mg kg^{-1})	11	176 ± 51**	3 ± 1** (64)	0 (0**)
WIN 44,441-2 (3 mg kg^{-1})	11	516 ± 169	21 ± 8 (82)	6 ± 5 (27)
Controls	15	1123 ± 177	66 ± 15 (100)	8 ± 5 (33)
Mr 1452 (1 mg kg^{-1})	9	462 ± 194	35 ± 19 (100)	2.3 ± 2.3 (22)
Mr 1452 (4 mg kg^{-1})	10	367 ± 152**	18 ± 10 (90)	0.1 ± 0.1 (10)
Mr 1452 (10 mg kg^{-1})	7	362 ± 159**	8 ± 5 (43)*	0 (0*)
Mr 1453 (4 mg kg^{-1})	10	809 ± 183	44 ± 16 (90)	1.3 ± 1 (20)
Mr 1453 (10 mg kg^{-1})	7	670 ± 169	34 ± 11 (86)	0.1 ± 0.1 (14)

* $P < 0.05$; ** $P < 0.01$

pharmacological properties of the stereoisomers used (H.W. Kosterlitz & H. Merz, personal communication; Ward *et al.*, 1983), the opioid receptor subtypes are most likely to be μ- and/or κ-types. Antagonism of the effects of endogenous opiates on presynaptic receptors on sympathetic nerves (e.g. von Kügelgen *et al.*, 1985) would be expected to enhance transmitter release (and result in increased rather than decreased ventricular ectopic activity). We suggest, therefore, that one likely site of action of Mr 1452 and WIN 44,441-3 is at the level of the sarcolemma, perhaps on ionic currents, especially as the antiarrhythmic effects of meptazinol in the same rat model can be accounted for by prolongation of action potential duration (Fagbemi *et al.*, 1982). It would seem important to determine the electrophysiological effects of selective opioid receptor activation and blockade in cardiac muscle.

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