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Arrhythmias induced by myocardial ischaemia-reperfusion are sensitive to ionotropic excitatory amino acid receptor antagonists

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Abstract

We have investigated the effects of (+)-5-methyl-10,11-dihydro-5H-dibenzo[*a*,*d*]cyclohepten-5,10-imine hydrogen maleate (MK801), a non-competitive *N*-methyl-D-aspartate (NMDA) ionotropic excitatory amino acid receptor antagonist, and 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX), a non-NMDA ionotropic excitatory amino acid receptor antagonist, ketamine and memantine, NMDA receptor channel blockers, on ventricular arrhythmias induced by myocardial ischaemia and myocardial ischaemia-reperfusion. Coronary artery occlusion caused 100 ± 2% ventricular tachycardia, in saline treated group, and 60 ± 3% ventricular fibrillation. 66 ± 6% of the animals recovered from ventricular fibrillation, while in 34 ± 4% of animals the ventricular fibrillation caused mortality. The incidence of ventricular tachycardia, ventricular fibrillation and mortality was not modified by treatment of rats with MK801 (0.3 mg/kg i.v.), CNQX (1 mg/kg i.v.), ketamine (10 mg/kg) and memantine (1.5 mg/kg), injected 5 min prior to occlusion. Reperfusion caused severe arrhythmias which started within 5 ± 2 s. For instance, in the saline treated group, the incidence of ventricular tachycardia was 100 ± 5%, while ventricular fibrillation occurred in 87 ± 3% of the animals and lasted 90 ± 12 s. The mortality was 62 ± 6%. The incidence of ventricular tachycardia, ventricular fibrillation and mortality induced by reperfusion was greatly ($P < 0.01$) reduced in animals treated with MK801 (0.3 mg/kg i.v.), CNQX (1 mg/kg i.v.), ketamine (10 mg/kg) and memantine (1.5 mg/kg), injected 5 min prior to occlusion. Therefore, reperfusion-induced arrhythmias, but not ischaemia-induced arrhythmias, are sensitive to NMDA/non-NMDA ionotropic excitatory amino acid receptor antagonists.

Keywords: Ischaemia; Reperfusion; Glutamate; Ionotropic; Excitatory amino acid; Receptor antagonist

1. Introduction

Numerous reports document the involvement of excitatory amino acids in the genesis of cardiac arrhythmias, mainly due to central effects (Cuparencu et al., 1990; Safta et al., 1990; Berrino et al., 1992). Similarly, numerous studies report that cardiac arrhythmias are sensitive to central excitatory amino acid receptor antagonists, particularly NMDA/non-NMDA subtype ones (Filippelli et al., 1994; Crambes et al., 1996). However, no study has been done concerning the effects of peripherally administered NMDA/non-NMDA receptor antagonists on the incidence of cardiac arrhythmias, especially those generated in conditions of cardiac disorders. Our study, therefore, investigated this in a model of cardiac disease, such as in vivo myocardial ischaemia. In particular, we investigated NMDA and non-NMDA excitatory amino acid receptor antagonists in ventricular arrhythmias induced by ischaemic myocardium and by ischaemic-reperfused myocardium. For this, we examined the effect of (+)-5-methyl-10,11-dihydro-5H-dibenzo[*a*,*d*]cyclohepten-5,10-imine hydrogen maleate (MK801), a non-competitive NMDA ionotropic excitatory amino acid receptor antagonist, and 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX), a non-NMDA ionotropic excitatory amino acid receptor antagonist, on ventricular arrhythmias induced by myocardial ischaemia and myocardial ischaemia followed by reperfusion. In addition, as NMDA ionotropic channel blocker resulted particularly effective in antagonizing arrhythmias induced by central administration of excitatory amino acids in animals with intact heart (Filippelli et al., 1994), we used ketamine, a blocker of the NMDA receptor at phencyclidine channel recognition site (Anis et al., 1983), and memantine, an other NMDA channel blocker (Bormann, 1989), to investigate the effects of NMDA ionotropic channel blockers on ventricular arrhythmias induced by myocardial ischaemia and ischaemia-reperfusion.

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2. Materials and methods

2.1. Surgical procedure

Male Sprague–Dawley rats (220–350 g) were anaesthetised with sodium pentobarbitone (60 mg/kg i.p.) and prepared for coronary artery occlusion by surgical techniques. Briefly, a femoral vein was cannulated to allow administration of further anaesthetic and drugs, a tra-cheotomy was performed to permit artificial ventilation (7025 Rodent Ventilator, Basile, Comerio, VA, Italy) when required, and a carotid artery was cannulated for blood pressure measurement. A left thoracotomy was performed and the pericardium removed to expose the heart. The heart was exteriorized briefly and a fine silk ligature (K802H, Ethicon, Pomezia, Roma, Italy) was placed around the left anterior descending coronary artery close to its origin. After the chest was opened by thoracotomy performed between the fourth and the fifth ribs approximately 3 mm from the sternum, the rats were ventilated artificially (Rodent Ventilator, Basile, Comerio, VA, Italy) with room air at a rate of 54 strokes min^{-1}, a stroke volume of 1.0 to 1.5 ml 100 g^{-1} and a positive end expiratory pressure of 0.5 to 1 cmH_2O. This was sufficient to maintain PCO_2 at 18–24 mmHg, PO_2 at 100–130 mmHg, and a pH within normal limits of 7.4 units. A lead 1 electrocardiogram (ECG) was monitored from subcutaneous stainless steel electrodes. Both the ECG and the blood pressure were continuously recorded on a Quartet polygraph (Basile, Comerio, VA, Italy). A rectal thermometer was inserted and the rats were kept at a body temperature of 37–38°C by an homeothermic blanket. In the study on ischaemia-inducing arrhythmias the ligature around the coronary artery was tied securely to induce permanent regional myocardial ischaemia. Arrhythmias were monitored for 25 min. Separate groups of rats were used to study ischaemia-reperfusion-inducing arrhythmias. In these rats, both ends of the ligature around the coronary artery were threaded through a small polythene button which was placed in contact with the heart. Coronary artery occlusion was achieved by applying tension to it and clamping the ligature against the button with a small, light weight, rubber-sheathed artery clip. After 5 min of myocardial ischaemia the clip was removed so that the tension on the ligature was released and reperfusion was allowed. Reperfusion-inducing arrhythmias were monitored for 8 min.

2.2. Parameters measured and arrhythmias analysis

In this study, mean arterial blood pressure was measured from the blood pressure trace. Heart rate (beats min^{-1}) was calculated from the ECG. Arrhythmia definitions were based on those detailed in the Lambeth Conventions. Ectopic activity was categorized as single ventricular premature beats (defined as discrete and recognisable premature QRS complexes in relation to the P wave, with a downward T wave), salvos (defined as a run of doublets and triplets in a row), ventricular tachycardia (4 or more consecutive ventricular premature beats occurring with clearly characterised R wave and a rate faster than sinus rhythm). These ventricular arrhythmias are associated with a decrease in blood pressure which is most pronounced during ventricular tachycardia. The total number of ventricular premature beats (including those occurring as ventricular tachycardia) that occurred during the first 25 min of permanent coronary artery occlusion or the first 8 min of reperfusion was calculated as the sum of the individual arrhythmias in animals that survived throughout the experiments. Ventricular fibrillation was defined when individual QRS complexes could not be longer distinguished, successive waves were inconsistent both in amplitude and in rhythm, and was accompanied by a sharp fall in blood pressure to zero mmHg with no pulse pressure. The incidence of ventricular tachycardia was recorded for each group and, as the rat can spontaneously recover from ventricular fibrillation, the incidence of reversible and irreversible ventricular fibrillation was noted. The onset time and the time spent in reversible ventricular fibrillation were also calculated. Mortality from irreversible ventricular fibrillation was also recorded.

2.2.1. Exclusion criteria

Experiments in which the following events occurred were excluded from the final data analysis: arrhythmias prior to coronary artery occlusion; mean arterial blood pressure less than 60 mmHg prior to drug or vehicle administration; heart failure during the first 5 min of ischaemia (i.e., progressive reduction in blood pressure towards zero indicating a non perfect surgical procedure). In reperfusion experiments two additional exclusion criteria were: reperfusion not evident (i.e., maintenance and/or progression of ECG changes typical of those occurring during sustained ischaemia); severe arrhythmias at 5 min post-occlusion thus preventing reperfusion.

2.3. Drugs

Were used sodium pentobarbitone, ketamine and memantine (Sigma, St. Louis, MO, USA), MK 801 (+)-5-ethyl- 10, 11-dihydro -5H- dibenzo[*a*,*d*]cyclohepten- 5,10-mine hydrogen maleate, CNQX (6-cyano-7-nitroquinoxaline-2,3-dione) (Research Biomedical, Natick, MA, USA). All drugs were dissolved in 0.9% NaCl (saline) while CNQX was dissolved in a minimal quantity of dimethylsulfoxide (DMSO) (1 mg/100 (l) and the final solution was brought to volume with 0.9% NaCl. Control injections were carried out with saline and saline solution of DMSO containing the same amount of DMSO in which CNQX was dissolved. All injections were made in a volume of 1 ml/kg.

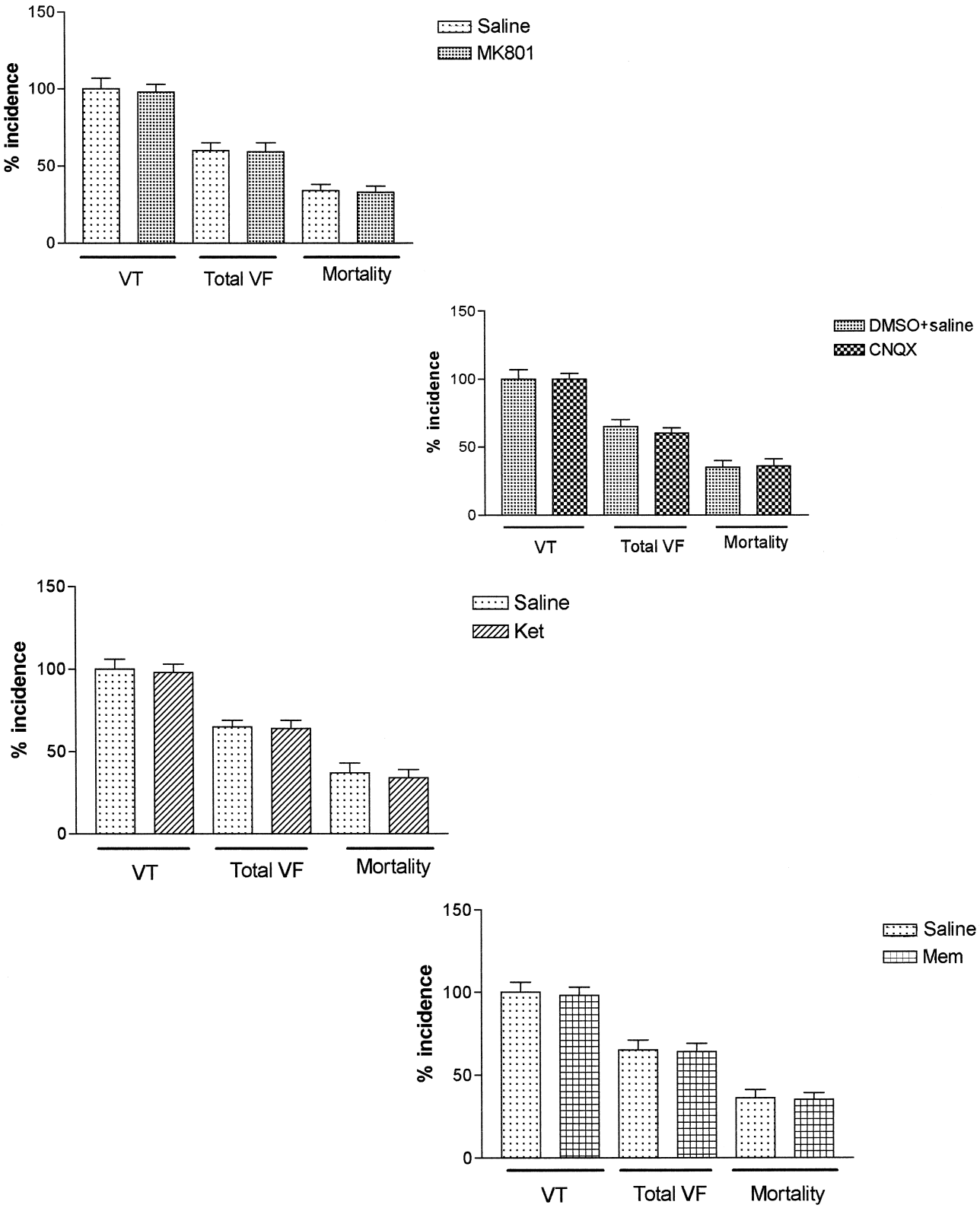

Fig. 1. The incidence of ischaemia-induced ventricular tachycardia (VT), total ventricular fibrillation (VF) and mortality (due to sustained VF) in control groups (saline and DMSO + saline), and in rats treated, 5 min prior to occlusion, with MK 801 (0.3 mg/kg), CNQX (1 mg/kg), ketamine (Ket; 10 mg/kg), and memantine (Mem; 1.5 mg/kg). Significant differences with control groups are shown as $* P < 0.05$.

2.4. Experimental protocol

Two separate arrhythmia studies were carried out. There were 6 different groups of rats in each study with $n = 6$ animals in each group. In each study, rats were allocated randomly to one of the 6 groups: control (saline; DMSO); MK801 (0.3 mg/kg); CNQX (1 mg/kg); ketamine (10 mg/kg) and memantine (1.5 mg/kg). Rats received drugs administered by intravenous bolus (1 ml/kg), and at doses chosen on the basis of previous works (Abrahams et al., 1993; Monassier et al., 1994; Matsumoto et al., 1995; Monassier et al., 1996). After 15 min of stabilization, the drug or vehicle administration was done 5 min prior to the coronary artery occlusion.

2.5. Statistical analysis

The incidence of ventricular tachycardia, ventricular fibrillation and mortality are expressed as a percentage and statistical significance assessed by using Fisher's Exact test. The number of ventricular premature beats are expressed as median (Q1–Q3) and compared by Mann–Whitney U-test. Mean arterial blood pressure and heart rate are expressed as mean ± S.E. and assessed within the group by One-way analysis of variance (ANOVA) and significant differences by Dunnett multiple comparison test. Mean arterial blood pressure and heart rate between groups were compared by two-tailed unpaired Student's *t*-test. A probability of $P < 0.05$ was considered to be significant.

3. Results

3.1. Ischaemia study

In the experiments on rats with permanent coronary artery occlusion, all the animals experienced ventricular tachycardia which, for instance in saline treated group, started 7.2 ± 1 min after the occlusion, while ventricular fibrillation occurred in 60 ± 3% of the animals (Fig. 1). 66 ± 6% of the animals recovered from ventricular fibrillation while in 34 ± 4% of animals the ventricular fibrillation caused mortality (Fig. 1). Coronary artery occlusion caused a significant ($P < 0.01$) transient fall in mean arterial blood pressure which was most pronounced at 3 min post-occlusion when mean arterial blood pressure fell of 29.8 ± 3% and 26.5 ± 4% in rats treated with saline and DMSO respectively (Table 1). Mean arterial blood pressure recovered towards pre-occlusion values after 25 min occlusion (Table 1). During coronary artery occlusion heart rate was decreased (Table 1). This decrease (e.g., saline, 4.9 ± 1.5%; DMSO, 4.7 ± 2% with respect to pre-occlusion values) became significant ($P < 0.05$) at 5 min post-occlusion in control groups, and it continued significantly ($P < 0.01$) during all the time of occlusion. For instance 25 min post-occlusion heart rate was decreased of 8.37 ± 2% in saline treated animals and 9.61 ± 3% in DMSO treated animals (Table 1). The incidence of ventricular tachycardia, ventricular fibrillation and mortality was not significantly modified by treatment of rats with MK801 (0.3 mg/kg i.v.), CNQX (1 mg/kg i.v.), ketamine (10 mg/kg) and memantine (1.5 mg/kg) injected 5 min prior to occlusion (Fig. 1). Similarly, the effects of coronary

Table 1
Changes in mean arterial blood pressure and heart rate during 25 min of coronary artery occlusion

	Pre-occlusion		Post-occlusion						
	− 5 min	0 min	1 min	3 min	5 min	10 min	15 min	20 min	25 min
Mean arterial blood pressure (mmHg ± S.E.)									
Control (Saline)	104 ± 4	104 ± 3	76 ± 4[b]	73 ± 3[b]	75 ± 3[b]	78 ± 4[b]	82 ± 4[b]	88 ± 3[b]	95 ± 4
Control (DMSO)	106 ± 3	102 ± 3	74 ± 4[b]	75 ± 3[b]	76 ± 3[b]	79 ± 4[b]	80 ± 4[b]	90 ± 3[a]	98 ± 4
MK 801	104 ± 4	102 ± 3	82 ± 4[b]	81 ± 3[b]	82 ± 4[b]	86 ± 3[b]	90 ± 4[a]	94 ± 3[a]	97 ± 4
CNQX	105 ± 3	105 ± 3	83 ± 3[b]	82 ± 4[b]	83 ± 3[b]	88 ± 4[b]	90 ± 4[a]	96 ± 3[a]	99 ± 4
Ket	103 ± 3	102 ± 4	80 ± 3[b]	79 ± 4[b]	80 ± 3[b]	84 ± 3[b]	88 ± 4[a]	90 ± 3[a]	98 ± 3
Mem	105 ± 5	104 ± 4	83 ± 4[b]	80 ± 3[b]	82 ± 4[b]	88 ± 4[a]	89 ± 5[a]	93 ± 3[a]	99 ± 3
Heart rate (beats min^{-1})									
Control (Saline)	384 ± 6	382 ± 4	376 ± 4	373 ± 5	365 ± 6[a]	358 ± 4[b]	355 ± 4[b]	355 ± 6[b]	350 ± 5[b]
Control (DMSO)	386 ± 5	385 ± 5	374 ± 4	375 ± 5	366 ± 4[a]	369 ± 4[a]	360 ± 5[b]	358 ± 5[b]	348 ± 4[b]
MK 801	380 ± 4	382 ± 4	382 ± 6	378 ± 5	371 ± 4[a]	366 ± 5[a]	361 ± 4[b]	354 ± 4[b]	342 ± 5[b]
CNQX	385 ± 5	385 ± 5	383 ± 4	380 ± 4	372 ± 3[a]	368 ± 4[b]	362 ± 5[b]	356 ± 5[b]	349 ± 4[b]
Ket	378 ± 4	378 ± 5	370 ± 3	369 ± 4	365 ± 4[a]	363 ± 3[a]	358 ± 4[a]	350 ± 4[b]	348 ± 5[b]
Mem	380 ± 5	384 ± 4	383 ± 5	380 ± 6	371 ± 4[a]	368 ± 5[a]	369 ± 5[a]	353 ± 4[b]	352 ± 5[b]

Changes in mean arterial blood pressure and heart rate recorded before and during 25 min of coronary artery occlusion in anaesthetized rats, $n = 6$, treated, 5 min prior to occlusion, with saline, DMSO, MK 801 (0.3 mg/kg), CNQX (1 mg/kg), ketamine (Ket; 10 mg/kg), and memantine (Mem; 1.5 mg/kg). The rats received drugs by intravenous bolus in a volume of 1 ml/kg. Significant differences with 0 min are indicated as [a]$P < 0.05$ and [b]$P < 0.01$. All groups were compared with group receiving saline, while CNQX group was compared with group receiving DMSO. In these groups no significant results were found.

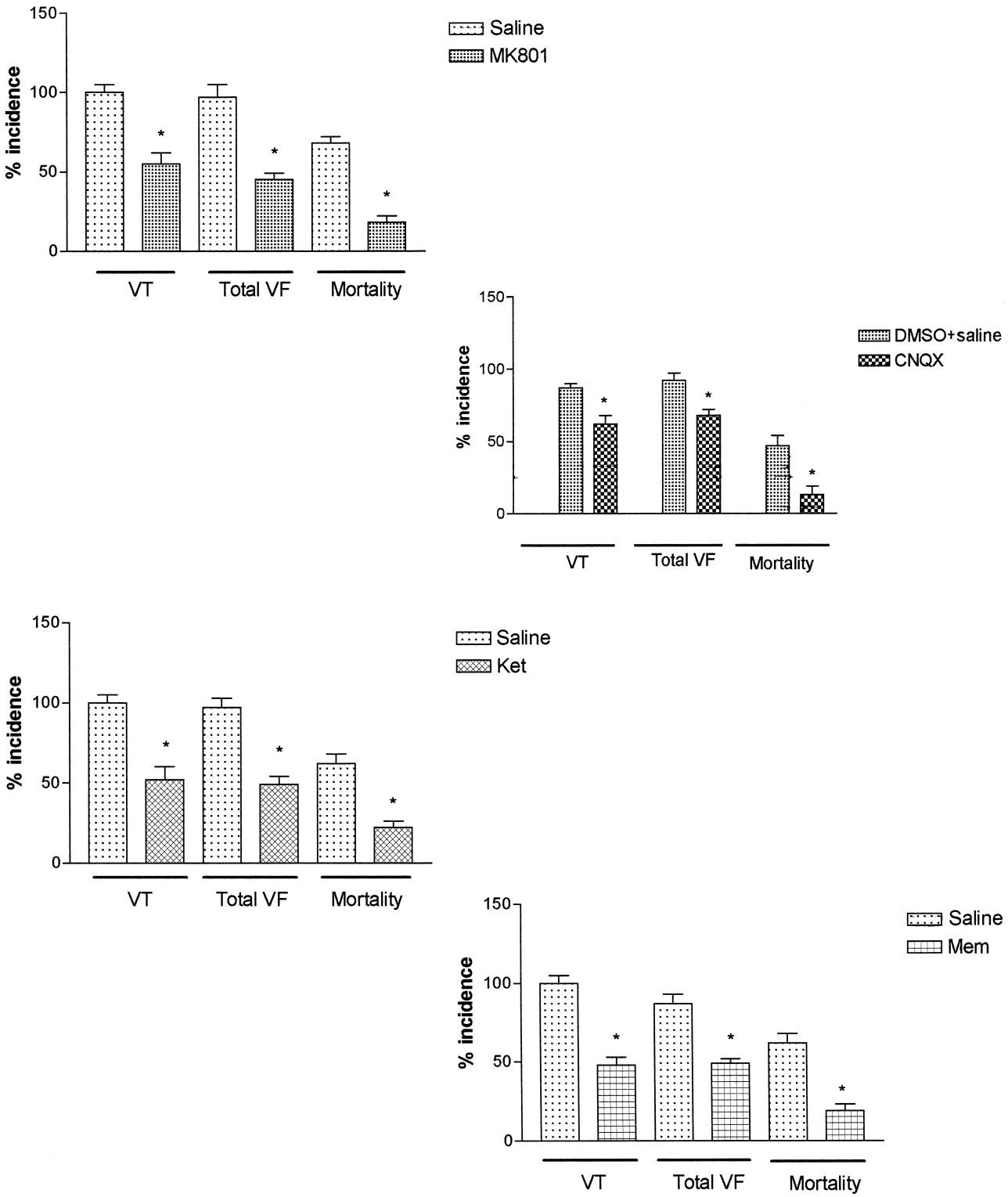

Fig. 2. The incidence of reperfusion-induced VT, total VF and mortality (due to sustained VF) in control groups (saline and DMSO + saline), and in rats treated, 5 min prior to occlusion, with MK 801 (0.3 mg/kg), CNQX (1 mg/kg), ketamine (Ket; 10 mg/kg), and memantine (Mem; 1.5 mg/kg). Significant differences with control groups are shown as $* P < 0.01$.

Table 2
Changes in mean arterial blood pressure and heart rate during 8 min reperfusion

	Pre-occlusion		Post-occlusion			Reperfusion	
	− 5 min	0 min	1 min	3 min	5 min	10 min	13 min
Mean arterial blood pressure (mmHg ± S.E.)							
Control (Saline)	106 ± 5	106 ± 4	78 ± 3[b]	74 ± 4[b]	75 ± 5[b]	89 ± 3[ac]	94 ± 3[d]
Control (DMSO)	104 ± 4	104 ± 3	77 ± 4[b]	73 ± 4[b]	76 ± 5[b]	89 ± 5[ac]	94 ± 4[d]
MK 801	103 ± 6	104 ± 4	85 ± 5[b]	80 ± 5[b]	79 ± 5[b]	100 ± 4[de]	102 ± 3[de]
CNQX	102 ± 3	107 ± 5	81 ± 4[b]	79 ± 4[b]	80 ± 5[b]	100 ± 3[de]	101 ± 1[ce]
Ket	105 ± 5	104 ± 4	80 ± 4[b]	77 ± 4[b]	76 ± 4[b]	98 ± 4[de]	103 ± 4[de]
Mem	105 ± 5	106 ± 5	80 ± 4[b]	78 ± 4[b]	78 ± 4[b]	97 ± 3[de]	104 ± 4[de]
Heart rate (beats min^{-1})							
Control (Saline)	380 ± 6	382 ± 5	377 ± 4	372 ± 4	360 ± 4[a]	365 ± 4	370 ± 3[c]
Control (DMSO)	384 ± 5	385 ± 5	373 ± 5	373 ± 4	365 ± 4[a]	370 ± 5	374 ± 3[c]
MK 801	379 ± 5	378 ± 4	380 ± 6	378 ± 5	365 ± 4[a]	373 ± 2[ce]	379 ± 3[ce]
CNQX	383 ± 5	384 ± 5	381 ± 4	380 ± 5	362 ± 3[a]	380 ± 2[ce]	381 ± 2[de]
Ket	381 ± 5	380 ± 4	379 ± 3	378 ± 3	368 ± 3[a]	380 ± 3[ce]	380 ± 3[ce]
Mem	382 ± 5	380 ± 4	381 ± 5	381 ± 6	369 ± 5[a]	381 ± 4[ce]	382 ± 4[ce]

Changes in mean arterial blood pressure and heart rate recorded before, during 5 min coronary artery occlusion and 8 min reperfusion in anaesthetized rats, $n = 6$. The rats were treated 5 min prior to occlusion with saline, DMSO, MK 801 (0.3 mg/kg), CNQX (1 mg/kg), ketamine (Ket; 10 mg/kg), and memantine (Mem; 1.5 mg/kg). The rats received drugs by intravenous bolus in a volume of 1 ml/kg. Significant differences with 0 min occlusion are indicated as [a]$P < 0.05$ and [b]$P < 0.01$. Significant differences with 5 min post-occlusion values are indicated as [c]$P < 0.05$ and [d]$P < 0.01$. All groups were compared with group receiving saline, while CNQX group was compared with group receiving DMSO. In these groups [e]$P < 0.05$ was considered significant.

artery occlusion on blood pressure and heart rate were not modified by these antagonists (Table 1).

3.2. Reperfusion study

Coronary artery occlusion caused arrhythmias which began 4 ± 1 min after ligature and consisted mainly of single ventricular premature beats. Reperfusion after 5 min of acute myocardial ischaemia caused severe arrhythmias which started within 5 ± 2 s. For instance, in saline treated group the incidence of ventricular tachycardia was 100 ± 5%, while ventricular fibrillation occurred in 87 ± 3% of the animals and lasted 90 ± 12 s (Fig. 2). The mortality was 62 ± 6% (Fig. 2). Reperfusion also recovered towards pre-occlusion values (saline, 106 ± 4 mmHg; DMSO, 104(± 3 mmHg) the transient fall (saline, −32 ± 4 mmHg; DMSO, −31 ± 3 mmHg) in mean arterial blood pressure induced by the previous occlusion. For instance, mean arterial blood pressure recovered of 89.6 ± 3% and 90.4 ± 5% 8 min after reperfusion in saline or DMSO treated groups, respectively (Table 2). During the ischaemia heart rate was significantly ($P < 0.05$) decreased of 5.2 ± 1% in saline treated animals and 4.8 ± 1% in DMSO treated animals at 5 min post-occlusion (Table 2). Heart rate recovered towards pre-occlusion values 8 min after reperfusion (Table 2). The recovery was 97.3 ± 2.7% and 97.3 ± 2.9% in saline or DMSO groups, respectively (Table 2). The incidence of ventricular tachycardia, ventricular fibrillation and mortality induced by reperfusion were greatly ($P < 0.01$) reduced in animals treated with MK801 (0.3 mg/kg i.v.), CNQX (1 mg/kg i.v.), ketamine (10 mg/kg) and memantine (1.5 mg/kg), injected 5 min prior to occlusion (e.g., the incidence was ventricular tachycardia: 55 ± 7%; ventricular fibrillation: 45 ± 4%; mortality: 8 ± 5% after MK801; ventricular tachycardia: 53 ± 8%; ventricular fibrillation: 47 ± 7%; mortality: 13 ± 6% after CNQX; ventricular tachycardia: 56 ± 6%; ventricular fibrillation: 48 ± 4%; mortality:10 ± 4% after ketamine; ventricular tachycardia: 52 ± 7%; ventricular fibrillation: 48 ± 6%; mortality: 10 ± 5% after memantine) (Fig. 2). These receptor antagonists also reduced the duration of ventricular fibrillation, which was 40 ± 9 s, 43 ± 11 s, 41 ± 7 s, 44 ± 8 s, for MK801, CNQX, ketamine and memantine respectively in saline group.

MK801, CNQX, ketamine and memantine, significantly ($P < 0.05$) increased the recovery of the fall in blood pressure and heart rate induced by occlusion (Table 2). After 8 min reperfusion, the increase of the recovery of blood pressure, respect to control groups, was 9.3 ± 1.4%, 9.5 ± 1.9%, 9.5 ± 2% and 9.3 ± 1.8%, for MK801, CNQX, ketamine and memantine, respectively. The increase of the recovery in heart rate, respect to control groups, was 3.1 ± 1%, 2.4 ± 0.9%, 2.5 ± 1.1% and 3.1 ± 0.8%, for MK801, CNQX, ketamine and memantine, respectively.

4. Discussion

Ventricular arrhythmias (e.g., tachycardia or ventricular fibrillation), are one of the most important causes of death in cardiovascular diseases. Different clinical situations may cause these arrhythmias, the most important of which is the myocardial ischaemia. Studies on anaesthetised rats have shown two distinct phases of post-occlusion ventricu-

lar arrhythmic activity (Parrat et al., 1981). The early phase of arrhythmias occurs within the first minutes of the occlusion, while the later phase of arrhythmias begins approximately hours after the occlusion or early after reperfusion. Our study shows that a permanent occlusion of the left anterior descending coronary artery, in rat, determines arrhythmias similarly to reperfusion which follows the coronary artery occlusion. Significant antiarrhythmic activity can be achieved by NMDA/non-NMDA excitatory amino acid receptor antagonists. In particular, these drugs may reduce the incidence of arrhythmias following reperfusion of the coronary artery. For example, in our study the antagonists MK801, a non-competitive NMDA receptor antagonist, CNQX, a non-NMDA receptor antagonist, ketamine and memantine, NMDA ionotropic channel blockers, reduce the incidence of ventricular tachycardia, ventricular fibrillation and reduced mortality. In contrast, these NMDA/non-NMDA receptor antagonists did not affect the incidence of arrhythmias (ventricular tachycardia and fibrillation), and mortality induced by occlusion of the coronary artery. Therefore, arrhythmias occurring in reperfusion but not in ischaemia are sensitive to NMDA/non-NMDA receptors antagonism. This is interesting since it underlines that arrhythmias occurring in reperfusion are supported by endogenous activation of excitatory amino acid receptors. It is tempting to speculate that under pathological conditions (i.e., during reperfusion) there is an increase in release of excitatory amino acids, similarly to that occurs in cerebral ischaemia-reperfusion (Sims and Zaidan, 1995). These could be arrhythmogenic and their activity could be expressed through NMDA/non-NMDA receptors.

It is not clear at the moment whether arrhythmias occur following the release at the level of the heart of excitatory amino acids, and whether they depend on cardiac excitatory amino acid receptors, but certainly there are evidences that intrinsic cardiac neurons are sensitive to excitatory amino acids and are involved in the genesis of arrhythmias (Huang et al., 1994), and evidences that excitatory amino acid receptors composed of both NMDA/non-NMDA subunits are present in cardiomyocytes of some mammals (Morhenn et al., 1994; Winter and Baker, 1995). The mechanism through which they could act still warrants further investigation, but it is well known that activation of ionotropic excitatory amino acid receptors leads an overload of $[Ca^{2+}]_i$ at level of cardiomyocytes (De Mello, 1985), which could alter the normal activity of these cells.

Our study also shows that during coronary artery occlusion and reperfusion added to arrhythmias we also have changes in blood pressure and heart rate. These effects during coronary artery occlusion were characterized by decrease in blood pressure and heart rate. These latter, in line with previous report using this model (Clark et al., 1980), suggest that during cardiac disorders, such as myocardial ischaemia, changes in blood pressure and heart rate does not follow schemes similar to that of intact heart. Indeed, it was expected to see an increase in heart rate in consequence of decrease in blood pressure. However, in our case, heart rate falls in coincidence with fall in blood pressure. Heart rate and blood pressure recover spontaneously at beginning of reperfusion, indicating that ischaemia plays an important role in maintaining the fall in blood pressure and consequent decrease in heart rate. In addition, this underscores that systemic haemodynamic changes could occur independently from arrhythmias, since these latters are properly generated and maintained during the reperfusion of coronary artery. Interestingly, the use of NMDA/non-NMDA receptor antagonists has increased the recovery of the effects on blood pressure and heart rate, as well as it induced recovery of arrhythmias. Excitatory amino acid receptor antagonists, therefore, act not only on arrhythmias, but also on hemodynamic changes induced by reperfusion.

In summary, the present study shows that peripheral administration of NMDA/non-NMDA excitatory amino acid receptor antagonists significantly reduces the incidence of ventricular tachycardia, total ventricular fibrillation, mortality and haemodynamic changes occurring in a model of myocardial ischemia-reperfusion in rats. The effect of NMDA/non-NMDA receptor antagonists is not evident during the ischaemia but it is evident during the reperfusion.

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