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MK-801 and memantine inhibit a centrally induced increase in myocardial oxygen demand in rabbits

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Abstract

Electrical stimulation of the paraventricular nucleus of the hypothalamus in the anaesthetized rabbit induces an increase in indexes of myocardial oxygen demand. This increase in myocardial oxygen demand is due to the activation of sympathetic pathways which include glutamatergic relays. In this model, systemic injection of dizolcipine (MK-801) and memantine inhibited these responses. Because these drugs have only one pharmacological property in common i.e. blockade of the NMDA receptor channel complex, these results fit with our previous results concerning the possible involvement of NMDA receptors in the central control of sympathetic activation. Memantine appears to be an interesting prototype for centrally acting cardioprotective drugs devoid of serious side effects.

Keywords: Paraventricular nucleus of the hypothalamus; Myocardial oxygen demand; MK-801; Memantine; (Rabbit)

1. Introduction

In a previous study, we reported that electrical stimulation of the paraventricular nucleus of the hypothalamus increased the myocardial oxygen demand by activating the sympathetic nervous system (Tibiriça et al., 1993). This response was inhibited by several drugs with NMDA receptor antagonist activity (Monassier et al., 1994). In addition, we observed that ketamine, a dissociative anaesthetic agent that acts on the phencyclidine channel recognition site of the NMDA complex (Anis et al., 1983), completely prevented the increase in myocardial oxygen demand but did not depress resting cardiac function. This ability to prevent central sympathetic activation in addition to a low cardiodepressive action is of potential interest. In the present study, we analysed the potential ability of two other NMDA channel blockers, namely dizolcipine and memantine, to reduce the cardiovascular consequences of central sympathetic stimulation. Dizolcipine (MK-801) exibits a very high affinity for the NMDA receptor channel complex (Javitt and Zukin, 1989) and is more selective for this receptor than ketamine. Memantine (1-amino-3,5-dimethyladamantane), which also displays NMDA channel antagonist properties (Bormann, 1989), is used as an antiviral drug and for the treatment of Parkinson disease (Chen et al., 1992). Here we describe some of the cardiovascular properties of MK-801 and memantine and we show that both drugs prevent the increase in myocardial oxygen demand caused by central sympathetic stimulation.

2. Materials and methods

Our rabbit model for a centrally induced increase in myocardial oxygen demand has been described extensively (Tibiriça et al., 1993; Monassier et al., 1994). Briefly, normotensive male rabbits (Zika strain) were anaesthetized with sodium pentobarbital (40 $mg \cdot kg^{-1}$) injected into the marginal vein of the ear. The animals were tracheotomized, immobilized with pancuronium bromide (1 $mg \cdot kg^{-1}$ i.v.) and artificially ventilated with room air (Hugo Sachs Elektronic model 6025, March-Hugstetten, Germany). The right femoral vein and artery were catheterized to perform i.v. injections and to measure arterial pressure through a catheter connected to a Statham P23 Db transducer which was, in turn, connected to a pressure

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processor and recorder (Gould Electronics model BS-272). Mean arterial pressure was calculated as the diastolic pressure plus one-third of the differential pressure. Heart rate was calculated from the rapidly recorded pressure signal and is given in beats per minute (bpm). Left ventricular pressure and the maximum rate of rise of left ventricular pressure (dP/dt_{max}) were measured with a micromanometer-tipped catheter (Gaeltec LTD, model ICT/B, Dunvegan, England) placed in the left ventricle via the right carotid artery. The dP/dt_{max} was obtained from a Philips differentiator model 133-1-4331. Two indexes of myocardial oxygen demand were calculated: the rate pressure product (RPP) and the triple product. The rate pressure product was calculated as the heart rate multiplied by the systolic blood pressure divided by 1000 to obtain convenient units, mm Hg · bpm · 10^{-3}, and the triple product (TP) was calculated as the RPP multiplied by dP/dt_{max} divided by 10^6 (TP expressed in mm $Hg^2 \cdot s^{-1} \cdot$ bpm · 10^{-6}).

A concentric bipolar stainless steel electrode (Rhodes Medical, model SNE-100) was used to stimulate the paraventricular nucleus of the hypothalamus. The stimulus (Hugo Sachs T stimulator) consisted of a 5 s train of 1 ms rectangular pulses at a frequency of 100 Hz with current intensities ranging from 100 to 200 μA (Hugo Sachs type 251 constant current unit, March Hugstetten, Germany), inducing dP/dt_{max} increases of about 30%.

The sites of stimulation were located according to the stereotaxic atlas of Sawyer et al. (1954), and the following coordinates were used: AP: +0.5 to +1 mm from bregma; L: −0.5 to −1 mm and V: −12 to −13 mm. A coronal section of the rabbit brain indicated the site of our electrical stimulation to be in the hypothalamus (Fig. 1).

Prior to any drug injection, at least 3 electrical stimulations at 5 min intervals were performed and averaged. When the haemodynamic responses obtained varied by less than 10% between 2 consecutive stimulations, the response was considered to be stable and the experiment was continued. At the end of each experiment, the site of stimulation was checked as described elsewhere (Tibiriça et al., 1993). Five min after the last stimulation of the control period, the first dose of the drug tested was injected. Its effects on resting parameters and during stimulation were evaluated 5 min later. The same procedure was repeated for each dose. In both experimental groups, drugs were injected intravenously in a cumulative manner. Slow bolus injections (10 s) were given. Maximal effects were observed, for both drugs, within 5 min of injection.

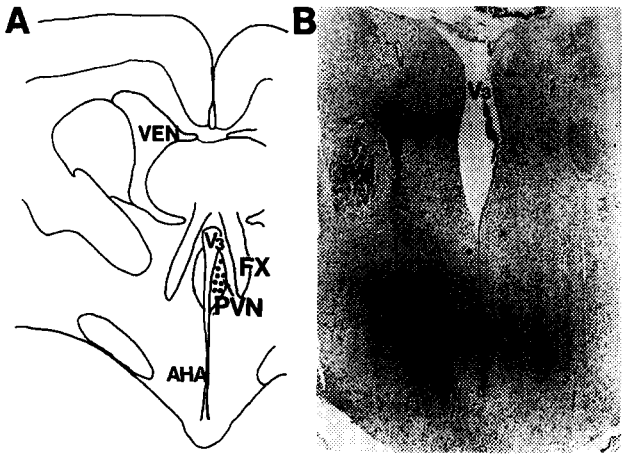

Fig. 1. Diagram (A) and photomicrograph (B) of a coronal section of the rabbit brain showing the sites of electrical stimulation in the paraventricular nucleus of the hypothalamus (PVN).

The following drugs were used: sodium pentobarbital (Abbott Lab., North Chicago, IL, USA); pancuronium bromide (Organon Tecknica, Fresnes, France); dizolcipine (MK801) (RBI, USA), memantine hydrochloride was a gift from Merz and Co, Frankfurt, Germany. MK801 and memantine were dissolved in normal saline solution (0.9% NaCl) for intravenous injection.

All results are expressed as means ± S.E.M. The effects of treatments on baseline haemodynamics and on the responses to electrical stimulation were analysed using two way analysis of variance for repeated measures (ANOVA)

Table 1
Effects of increasing doses of intravenous MK-801 on basal haemodynamics and on the cardiovascular responses to electrical stimulation of the paraventricular nucleus of the hypothalamus of pentobarbital-anaesthetized rabbits

MK 801 doses	0		0.1		0.3		1	
mg · kg^{-1} i.v.	C1	S1	C2	S2	C3	S3	C4	S4
SAP (mm Hg)	118 ± 8	148 ± 9	112 ± 11	135 ± 13	98 ± 10	112 ± 13 [a]	93 ± 7 [b]	99 ± 9 [a]
DAP (mm Hg)	90 ± 6	121 ± 7	85 ± 9	110 ± 13	73 ± 8	91 ± 13 [a]	69 ± 7	77 ± 10 [a]
MAP (mm Hg)	99 ± 7	130 ± 8	94 ± 10	119 ± 13	81 ± 9	98 ± 13 [a]	77 ± 7	84 ± 9 [a]
HR (beats · min^{-1})	278 ± 17	275 ± 14	281 ± 17	277 ± 18	283 ± 16	281 ± 16	276 ± 16	271 ± 15
dP/dt_{max} (mm Hg · s^{-1})	3641 ± 410	4562 ± 460	3504 ± 551	4307 ± 611	3071 ± 492	3700 ± 595 [a]	2957 ± 427	3193 ± 459 [a]
RPP (× 10^{-3})	32 ± 2	40 ± 2	32 ± 4	37 ± 4	27 ± 3	31 ± 4 [a]	25 ± 2	26 ± 2 [a]
TP (× 10^{-6})	123 ± 23	189 ± 28	122 ± 32	176 ± 40	93 ± 25	129 ± 34 [a]	81 ± 19	90 ± 19 [a]

C = baseline values: S = electrical stimulation. Each value represents the mean ± standard error of the mean of 7 experiments. [a] $P < 0.05$: statistically significant effect of electrical stimulation when compared to values for stimulation before treatment (S1); [b] $P < 0.05$: significant effect of the treatment on basal cardiovascular parameters when compared to control values (C1) (ANOVA for repeated measures followed by Scheffé's test). SAP, systolic arterial pressure; DAP, diastolic arterial pressure; MAP, mean arterial pressure; HR, heart rate; RPP, rate pressure product; TP, triple product.

followed by Scheffé's test to detect statistically significant differences. All calculations were made by computer-assisted analyses with the Statview II program (Abacus Concepts, Berkeley, USA).

3. Results

3.1. Effects of electrical stimulation of the paraventricular nucleus of the hypothalamus

As observed in 12 male rabbits, the electrical stimulation of the paraventricular nucleus of the hypothalamus increased arterial blood pressure during the period of stimulation. Systolic blood pressure increased from 119 ± 5 to 149 ± 6 mm Hg ($P < 0.05$). dP/dt_{max} increased from a basal value of 3815 ± 284 to 4737 ± 334 mm Hg/s during stimulation ($P < 0.05$). Heart rate was not modified during stimulation of the paraventricular nucleus of the hypothalamus. As a consequence, the cardiac oxygen consumption indexes were also increased: RPP increased from 34 ± 2 to 41 ± 2 ($P < 0.05$) and the TP from 134 ± 15 to 203 ± 19 ($P < 0.05$).

3.2. Effects of cumulative intravenous doses of MK-801

As shown in Table 1, MK-801 (0.1, 0.3 and 1 mg · kg^{-1}) dose dependently reduced the haemodynamic response to the stimulation of the paraventricular nucleus of the hypothalamus. The myocardial oxygen demand indexes were significantly reduced by the 0.3 and 1 mg · kg^{-1} doses. The value of RPP during stimulation decreased from a basal level of 40 ± 2 to 31 ± 4 and 26 ± 2, respectively, while the triple product decreased from 189 ± 28 to 129 ± 34 and 90 ± 19 ($P < 0.05$; $n = 7$). Basal haemodynamics were not significantly influenced by the drug, with the exception of the resting systolic blood pressure, which was reduced by the highest dose from a pretreatment value of 118 ± 8 mm Hg to 93 ± 7 mm Hg ($P < 0.05$). A complete recovery of the response was obtained about 35 min after the injection of the highest dose of MK-801.

3.3. Effects of cumulative intravenous doses of memantine

As detailed in Table 2, increasing doses of memantine (1, 5 and 10 mg · kg^{-1}) decreased the peak values of blood pressure, heart rate and cardiac dP/dt_{max} reached during electrical stimulation of the paraventricular nucleus of the hypothalamus. At the highest dose, the peak values of blood pressure and cardiac contractility were significantly reduced. As a consequence, the myocardial oxygen demand indexes were diminished during stimulation. The RPP decreased from 45 ± 2 to 26 ± 4 ($P < 0.05$; $n = 5$) while the TP decreased from 223 ± 25 to 80 ± 15 ($P < 0.05$). At this active dose, the basal haemodynamics were also affected. The basal mean arterial blood pressure was lowered from 102 ± 6 to 70 ± 13 mm Hg while dP/dt_{max} was decreased from 4060 ± 393 to 2080 ± 549 mm Hg/s. Neither the basal values of the heart rate, nor the heart rate values recorded during stimulation, were significantly affected by memantine. A complete recovery of the response was obtained about 15 min after the injection of the highest dose of memantine.

4. Discussion

As previously described, the electrical stimulation of the paraventricular nucleus of the hypothalamus increases arterial blood pressure and cardiac contractility (as evaluated by the index dP/dt_{max}) (Monassier et al., 1994). This results in an increase of the RPP and of the TP, two indexes which are closely correlated to a direct measure of myocardial oxygen demand (Baller et al., 1979). In this model, NMDA receptor antagonists were shown to potently attenuate these haemodynamic responses, some of the antagonistst were devoid of any cardiodepressive properties (Monassier et al., 1994).

Table 2
Effects of increasing doses of intravenous memantine on basal haemodynamics and on the cardiovascular responses to electrical stimulation of the paraventricular nucleus of the hypothalamus of pentobarbital-anaesthetized rabbits

Memantine doses	0		1		5		10	
mg · kg^{-1} i.v.	C1	S1	C2	S2	C3	S3	C4	S4
SAP (mm Hg)	120 ± 7	150 ± 9	111 ± 14	130 ± 14	106 ± 14	121 ± 16	85 ± 13	94 ± 13 [a]
DAP (mm Hg)	93 ± 6	127 ± 7	84 ± 12	107 ± 12	81 ± 13	99 ± 15	62 ± 13 [b]	74 ± 14 [a]
MAP (mm Hg)	102 ± 6	135 ± 8	93 ± 13	115 ± 13	89 ± 13	107 ± 15	70 ± 13 [b]	81 ± 14 [a]
HR (beats · min^{-1})	309 ± 10	303 ± 16	304 ± 11	302 ± 14	300 ± 17	296 ± 16	280 ± 5	282 ± 8
dP/dt_{max} (mm Hg · s^{-1})	4060 ± 393	4983 ± 515	3670 ± 601	4380 ± 662	3620 ± 717	4130 ± 765	2080 ± 549 [b]	2950 ± 428 [a]
RPP (×10^{-3})	37 ± 2	45 ± 2	34 ± 5	39 ± 5	32 ± 5	36 ± 6	24 ± 4 [b]	26 ± 4 [a]
TP (×10^{-6})	150 ± 18	223 ± 25	133 ± 29	180 ± 39	127 ± 35	163 ± 47	65 ± 13 [b]	80 ± 15 [a]

C = baseline values: S = electrical stimulation. Each value represents the mean ± standard error of the mean of 5 experiments. [a] $P < 0.05$: statistically significant effect of electrical stimulation when compared to values for stimulation before treatment (S1); [b] $P < 0.05$: significant effect of the treatment on basal cardiovascular parameters when compared to control values (C1) (ANOVA for repeated measures followed by Scheffé's test). SAP, systolic arterial pressure; DAP, diastolic arterial pressure; MAP, mean arterial pressure; HR, heart rate; RPP, rate pressure product; TP, triple product.

In our previous study, we showed that ketamine (a dissociative anaesthetic drug) was one of the most active drugs tested in our experimental model and did not cause cardiovascular depression. The pharmacological mechanism underlying this effect of ketamine is probably the blockade of NMDA receptors in the central sympathetic pathways. In this paper we were interested in testing the cardiovascular actions of two drugs which are able to block the same receptor channel complex as ketamine in our experimental model, i.e. MK-801 (dizolcipine) and memantine (Bormann, 1989; Chen et al., 1992; Kornhuber et al., 1989).

Dizolcipine (MK-801) has been shown to be very potent in different experimental models of epilepsy and of cerebral ischaemia (Hatfield et al., 1992). Nevertheless, its low therapeutic index prevents its clinical use, especially in chronic treatments. In fact, this compound induces several adverse effects such as circling behaviour and memory dysfunctions (Tricklebank et al., 1989). In contrast, memantine is currently used as an antiviral agent and as an anti-Parkinsonian drug and is devoid of deleterious side effects. This substance is also effective in experimental models of cerebral ischaemia (Nasr et al., 1990) and has been used in post traumatic cerebral coma in humans (Von Miltner, 1982). Furthermore, memantine displays a cytoprotective action which is also attributed to its NMDA channel blocking properties (Bormann, 1989).

In our experimental model in the anaesthetized rabbit, memantine and MK-801 proved to be effective in preventing the centrally induced increase in myocardial oxygen demand. Because the only property that MK-801 and memantine have in common is antagonism of NMDA receptors, one can assume that this mechanism accounts for this action of both compounds. However, MK-801 elicited less hypotensive and negative inotropic effects than memantine. That MK-801 did not cause cardiovascular depression is in contrast with other previously published data. MK-801 is hypertensive, especially after intravenous injection, in conscious rats but at much higher doses than those used here (50–250 × our highest dose) (Lewis et al., 1989). The same results have been obtained with the same range of doses as those used in this study but in chloralose-anaesthetized cats (Abrahams et al., 1993). These low cardiovascular repercussions of MK-801, in our model, are in contrast with the effects of the other NMDA receptor antagonist memantine. Whether or not these hypotensive and negative cardiac inotropic effects of memantine are additional pharmacological properties of this compound remains unclear (Spanagel et al., 1994; Von Maj, 1982; Von Sontag et al., 1982; Von Wesemann et al., 1983). In any case, due to the fact that this drug appears to be well tolerated in humans, one can assume that it does not cause important cardiodepression, at least at the dose levels used in humans. Nevertheless, this latter point needs confirmation in animals and is currently under investigation in conscious rabbits.

These results fit in with our previous data concerning the cardiovascular effects of drugs with NMDA receptor antagonist activity. In this model, MK-801 appeared to be the most interesting drug because it inhibited the haemodynamic response to electrical stimulation of the paraventricular nucleus of the hypothalamus without causing marked cardiodepression. Thus, the cardiovascular effects of MK-801 appeared very similar to those we reported for ketamine elsewhere (Monassier et al., 1994). The cardiovascular profile of memantine and in particular its apparent safety in humans make this molecule even more attractive as a prototype for centrally acting cardioprotective drugs. In this respect, the lack of deleterious cardiodepressive actions in unanaesthetized animal models has yet to be documented. Experiments are in progress to clarify the site(s) of action of these two molecules. Although it is likely that the cardiovascular effects of MK-801 and memantine largely originate within the central nervous system, a peripheral contribution to these effects cannot be discounted.

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