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Participation of NMDA and kainate receptors of paraventricular nucleus in cardiovascular responses to glutamate receptor agonist

M. Zafer Gören, Filiz Onat, Kemal Berkman *

Marmara University, School of Medicine, Department of Pharmacology and Clinical Pharmacology, Haydarpaşa, Istanbul, TR 81326, Turkey

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Abstract

The nuclei of the hypothalamus have been shown to be involved in central cardiovascular homeostasis. Recent studies suggest that glutamate-containing neurons have an important role in the regulation of central cardiovascular function. We report first on the effects of intracerebrally injected NMDA and non-NMDA receptor ligands on blood pressure and heart rate in conscious Sprague–Dawley rats. In the second part, we describe the effect of blockade of NMDA or kainate receptors in the paraventricular nucleus on glutamate receptor agonist-induced blood pressure responses. Intracerebroventricular injections of L-glutamic acid, NMDA and kainic acid produced increases in mean arterial pressure. Kainic acid produced significant decreases in heart rate. Microinjection of DL-2-amino-5-phosphonopentanoic acid (APV; 25 and 50 nmol), a competitive NMDA receptor antagonist, into the paraventricular nucleus blunted the increases in the mean arterial pressure evoked by intracerebroventricular injections of NMDA (1 nmol), whereas microinjection of dinitroquinoxaline (DNQX; 20, 40 and 80 pmol), which acts as an antagonist at kainate receptors, failed to antagonize the cardiovascular effects of intracerebroventricular kainic acid (10 pmol). Microinjections of NMDA (100 pmol) into the paraventricular nucleus produced pressor responses, but kainic acid (5 and 10 pmol) failed to affect either mean arterial pressure or heart rate. These results suggest participation of the glutamergic system in cardiovascular regulation via NMDA receptors located within the paraventricular nucleus of the hypothalamus in rats.

Keywords: Paraventricular nucleus; Excitatory amino acid; Cardiovascular regulation; Central; Microinjection; (Rat)

1. Introduction

Glutamate and its receptors play important roles in central cardiovascular regulation (Sundaram et al.,1989; Soltis and Di Micco, 1991, 1992; Porter, 1993). It has been shown that systemic administration of excitatory amino acid receptor blockers produces cardiorespiratory effects in α-chloralose anesthetized cats (Abrahams et al., 1993). The majority of the autonomic nerves that regulate heart rate and blood pressure originate from the specialized nuclei in the spinal cord (Dampney, 1994). Different nuclei found in the brain stem and the hypothalamus form the sympathetic premotor neurons by direct projections to the preganglionic autonomic neurons (Stack et al., 1986, 1989). The rostral ventrolateral and ventromedial medulla, A5 noradrenergic region in caudal ventrolateral pons and caudal raphe nucleus are distinguished as groups of specialized nuclei, known as the sympathetic premotor neurons (Dampney, 1994). Likewise, the paraventricular nucleus of the hypothalamus, as a forebrain structure, contains sympathetic premotor neurons (Saper et al., 1976; Luiten et al., 1985; Dampney, 1994). Parvocellular elements of the paraventricular nucleus project to the hindbrain and spinal cord, and magnocellular vasopressinergic neurons project to the median eminence and posterior pituitary (Saper et al., 1976; Swanson and Sawchenko, 1984). Both chemical and electrical stimulation of the paraventricular nucleus produces cardiovascular effects in various species (Gören et al., 1996, 1997). Chemical stimulation of the paraventricular nucleus in conscious rats by glutamate elevated heart rate and arterial blood pressure, together with increases of plasma epinephrine and norepinephrine levels (Martin and Haywood, 1992). In addition, electrical stimulation of the paraventricular nucleus in rabbits under pentobarbital anesthesia produced a positive inotropic effect and increases in blood pressure and myocardial oxygen demand (Monassier et al., 1994). These effects were antago-

* Corresponding author. Tel.: +90-216-349-2816; fax: +90-216-347-5594.

E-mail address: fonat@escortnet.com (K. Berkman).

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nized by intracerebroventricular administration of NMDA receptor antagonist dichlorokynurenic acid, and NMDA receptor competitive antagonist aminophosphonovalerate (APV) and intravenous ketamine, a non-competitive NMDA receptor antagonist (Monassier et al., 1994). It is obvious that the paraventricular nucleus elicits cardiovascular responses by affecting autonomic functions. The pressor response associated with electrical stimulation of the paraventricular nucleus in anesthetized cats was postulated to involve a vasopressin component in the central cardiovascular regulation (Ciriello and Calaresu, 1980). The role of the paraventricular nucleus in excitatory amino acid-mediated cardiovascular regulation, however, needs further studies. The present study was designed to evaluate the effects of administration of ionotropic glutamate receptor agonists, either intracerebroventricularly or into the paraventricular nucleus, on cardiovascular parameters and the effects of blockade of NMDA and kainate receptor subtypes by injection of the antagonists directly into the paraventricular nucleus on the glutamate receptor agonist-induced blood pressure and heart rate responses in conscious rats.

2. Materials and methods

2.1. Animals

Sprague–Dawley rats, weighing 200–250 g of both sexes were used in the study. The rats were housed in a temperature-controlled room (21 ± 3°C) with an alternating 12-h light/dark cycle, and water and food ad libitum. All procedures with the animals were performed using humane methods under the license of the university ethical committee for laboratory animals.

2.2. Surgery

Three to four days before the experiments, the rats were anesthetized with a mixture of ketamine at a dose of 100 mg/kg, and chlorpromazine at a dose of 1.0 mg/kg. The head of the rat was placed on a stereotaxic frame (Stoelting Model 51600, USA). In the first series of experiments, a stainless guide cannula (Plastics One, System C313G, USA) was placed into the lateral ventricle according to the stereotaxic atlas of Paxinos and Watson (1986). The coordinates for the intracerebroventricular cannula were 1.5 mm lateral and 1 mm posterior to the bregma and 3.4 mm deep from the skull surface. In the next series of experiments, a parenchymal guide cannula (32 gauge, Plastics One, System C315G) was inserted into the paraventricular nucleus of the hypothalamus. The paraventricular nucleus coordinates for the parenchymal cannula were 0.5-mm lateral and 2.4-mm posterior from the bregma and 7 mm-deep from the surface of the skull. The guide cannula was 1-mm shorter than the internal parenchymal or intracerebroventricular cannula. Trigonometric calculations of the intracerebroventricular coordinates with an angle of 10° to the coronal plane were carried out for the coordinates of the intracerebroventricular and intracerebral parenchymal guide cannula in the same rat. Two additional supporting screws were also placed onto the skull and all the canulae and screws were secured with dental acrylic cement. After completion of the stereotaxic surgery, the intracerebroventricular or the parenchymal guide cannula was plugged by suitable dummy caps with stylets. These dummy caps were removed and an internal parenchymal or intracerebroventricular cannula filled with drug solutions was inserted through the guide cannula on the day of experiments. Each rat received single intracerebroventricular injection or parenchymal microinjection with or without pretreatment.

2.3. Drug solutions

L-glutamic acid (Sigma, USA) solutions were prepared and buffered to pH 7.4 and serial dilutions were made with physiological saline. NMDA (Sigma), APV (DL-2-amino-5-phosphonopentanoic acid; Sigma), kainic acid (2-carboxy-3-carboxymethyl-4-isopropenylpyrrolidine; Sigma) solutions were prepared and diluted daily with physiological saline (0.9% NaCl) for the chosen doses. Only 6,7-dinitroquinoxaline-2,3(1H,4H)-dione (DNQX) stock solutions were prepared with 5% β-cyclodextrin (Selectochemie, Switzerland) solution and diluted with physiological saline thereafter, prior to injections.

2.4. Blood pressure and heart rate recordings

Continuous blood pressure and heart rate measurements were made directly using polyethylene catheters (PE-10 attached to PE-50) inserted into the right iliac artery under ether anesthesia. Polyethylene catheters were exteriorized through the neck and connected to a pressure transducer (Grass, USA). Pulse changes were amplified through a polygraph (Grass, Model 7) and a tachograph (Grass, Model 7P44D). The animals were placed in Plexiglas cages ($25 \times 25 \times 30$ cm), and the injections were performed after a stabilization period of 2–3 h. Injection stylets extending 1 mm below the tips of the guide cannula were inserted for intracerebroventricular and/or parenchymal administration of the test compounds contained within the attached polyethylene tubing.

2.5. Study design

In the first series of experiments, cardiovascular responses to intracerebroventricular administration of saline ($n = 8$), L-glutamic acid (0.5 μmol, $n = 8$; 1 μmol, $n = 8$), NMDA (0.5 nmol, $n = 8$; 1 nmol, $n = 8$) or kainic acid (5 pmol, $n = 7$; 10 pmol, $n = 6$) were determined in conscious rats. In the second series of experiments, cardiovascular responses to intracerebroventricular injection of

NMDA (1 nmol, $n = 4$ each group) or kainic acid (10 pmol, $n = 5$ each group) in APV- or DNQX-pretreated animals were studied in conscious rats. In the last series of experiments, NMDA (50 pmol, $n = 6$; 100 pmol, $n = 6$) or kainic acid (0.1 pmol, $n = 6$; 0.5 pmol, $n = 6$) was injected into the paraventricular nucleus of the hypothalamus.

2.6. Injections

Intracerebroventricular injections were given in a volume of 10 μl with the aid of a 20-μl Hamilton microsyringe, whereas intracerebral parenchymal microinjections were given in a volume of 200 nl through a parenchymal cannula with a 0.5-μl Hamilton microsyringe. Pretreatment with APV or DNQX administration into the paraventricular nucleus of the hypothalamus was performed 5-min before intracerebroventricular injection of NMDA or kainic acid, respectively. The injections were performed within 20 s with a microinjection pump (Kd Scientific, USA).

2.7. Histology

Only data from histologically verified intracerebral parenchymal microinjections were included in the study. For this purpose, the rats were anesthetized with urethane and 200-nl methylene blue was injected through the cannula. Transcardiac 10% formalin was infused at the end of each experiment before killing. Forty-micrometer coronal sections of the brain were made with an under cryostat at −20°C (Microm, Germany). The slides were then stained with thionine, and the localization of the injection site was verified under a surgical light microscope (Fig. 1). Spots within the area of the paraventricular nucleus were accepted as verified. If diffusion of the dye into other areas was observed in coronal sections, the data from those subjects were excluded. Intracerebroventricular injections were verified by administration of 10-μl methylene blue through the cannula and diffusion of the dye into the ventricles and aquaduct was checked after decapitation.

2.8. Data analysis

The blood pressure recordings were converted into mean arterial pressure with the following formula: mean arterial pressure = (pulse pressure/3) + diastolic pressure. All results were expressed as means ± standard error of mean (SEM). One-way analysis of variance (ANOVA) followed by multiple comparison with Duncan's multiple range test was used to analyze the effects of microinjections of single

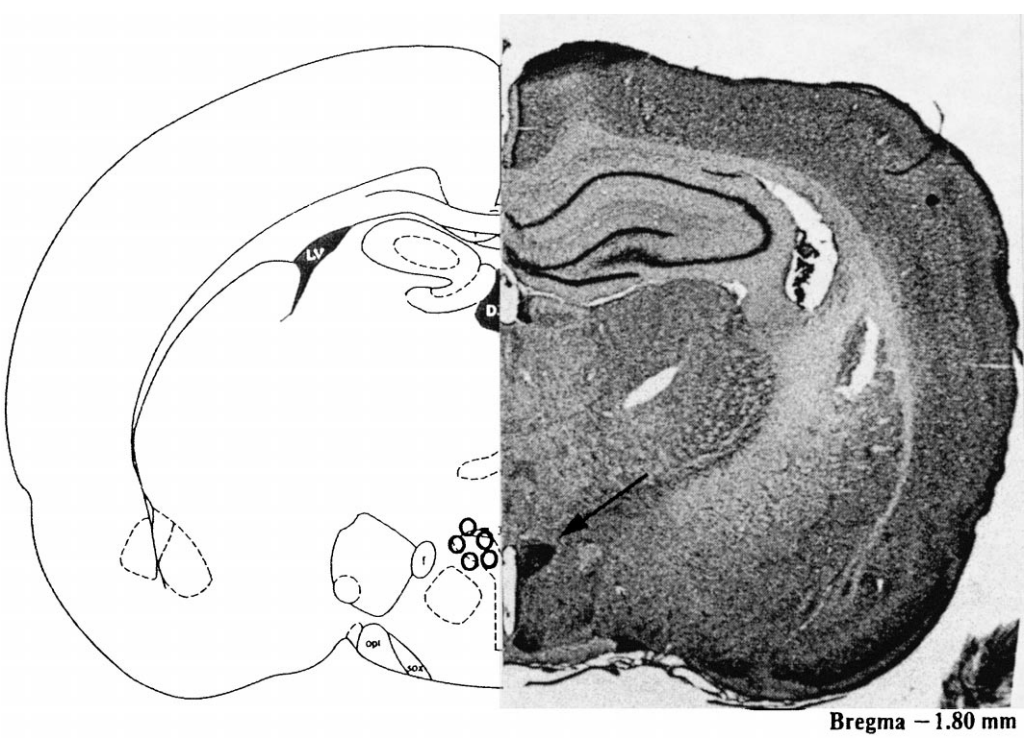

Fig. 1. A representative coronal section and photomicrograph of the region of the paraventricular nucleus (−1.80-mm posterior to bregma). Arrow indicates paraventricular nucleus. O, microinjection sites in DNQX pretreatment group; opt, optic tract; sox, supraoptic decussation; LV, lateral ventricle; f, fornix.

Table 1
Time course of mean arterial pressure (MAP; mm Hg) and heart rate (HR; beats/min) after injection of glutamate receptor agonists either intracerebroventricularly (i.c.v.) or into the paraventricular nucleus of the hypothalamus (PVN)
Values are expressed as means ± SEM.

Treatment		Time (min)											
		Basal		1		3		5		10		30	
		MAP	HR	MAP	HR	MAP	HR	MAP	HR	MAP	HR	MAP	HR
L-Glutamate (i.c.v.)	0.5 μmol	100 ± 2	364 ± 11	110 ± 2[a]	320 ± 11	112 ± 4[a]	338 ± 17	109 ± 4[a]	344 ± 13	102 ± 2	354 ± 12	101 ± 2	367 ± 14
L-Glutamate (i.c.v.)	1 μmol	97 ± 3	355 ± 13	115 ± 6[a]	306 ± 15	113 ± 5[a]	326 ± 19	112 ± 3[a]	304 ± 17	103 ± 3	319 ± 21	101 ± 4	350 ± 20
NMDA (i.c.v.)	0.5 nmol	99 ± 2	368 ± 4	107 ± 2[a]	391 ± 8	109 ± 2[a]	404 ± 11	105 ± 2	396 ± 9	104 ± 2	396 ± 9	101 ± 4	388 ± 5
NMDA (i.c.v.)	1 nmol	100 ± 1	361 ± 11	116 ± 2[a]	364 ± 22	114 ± 3[a]	379 ± 32	107 ± 2[a]	378 ± 31	103 ± 2	384 ± 15	102 ± 1	400 ± 15
Kainic acid (i.c.v.)	5 pmol	99 ± 1	369 ± 6	111 ± 2[a]	326 ± 11	108 ± 2[a]	329 ± 11	107 ± 2	326 ± 11	107 ± 2	326 ± 9	100 ± 1	350 ± 15
Kainic acid (i.c.v.)	10 pmol	102 ± 1	371 ± 4	118 ± 1[a]	303 ± 10[a]	113 ± 2[a]	298 ± 8[a]	109 ± 2[a]	303 ± 10[a]	107 ± 2	308 ± 13[a]	101 ± 2	381 ± 16
NMDA (PVN)	50 pmol	96 ± 2	346 ± 17	103 ± 2	359 ± 19	105 ± 2	377 ± 26	103 ± 3	363 ± 15	100 ± 3	359 ± 18	98 ± 2	355 ± 16
NMDA (PVN)	100 pmol	99 ± 2	353 ± 12	110 ± 4[a]	370 ± 18	110 ± 4[a]	378 ± 19	110 ± 4[a]	379 ± 23	104 ± 5	359 ± 17	102 ± 4	344 ± 12
Kainic acid (PVN)	0.1 pmol	96 ± 1	368 ± 2	99 ± 1	334 ± 26	102 ± 1	346 ± 23	99 ± 2	356 ± 18	97 ± 1	344 ± 20	94 ± 1	360 ± 18
Kainic acid (PVN)	0.5 pmol	97 ± 2	351 ± 11	100 ± 3	338 ± 8	101 ± 2	356 ± 13	102 ± 2	366 ± 24	101 ± 2	353 ± 8	95 ± 2	338 ± 13

[a] Indicates significance of difference from baseline levels using one-way ANOVA followed by the post-hoc test of Duncan, $P < 0.05$.

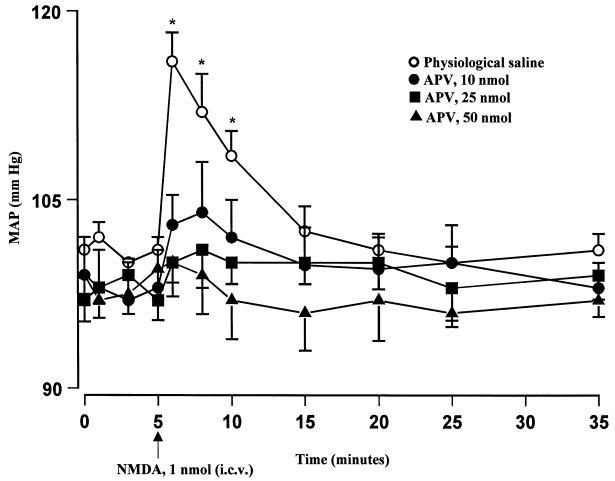

Fig. 2. Blood pressure responses to intracerebroventricular injection of NMDA in APV- (10, 25 and 50 nmol) or saline-pretreated animals. Values represent means ± SEM. Asterisks indicate significance of differences from baseline levels, using one-way ANOVA followed by the post-hoc test of Duncan. * $P < 0.05$.

treatments. Two-way ANOVA was used for the comparison of the groups receiving different treatments.

3. Results

3.1. Cardiovascular responses to intracerebroventricular administration of saline, L-glutamic acid, NMDA or kainic acid

Intracerebroventricular injection of physiological saline solution produced no change in mean arterial pressure, whereas L-glutamic acid at 0.5- and 1-μmol doses produced increases in mean arterial pressure, reaching maximum values within the first 5 min (Table 1). The increases in mean arterial pressure returned to their basal levels within 20 min. When Duncan's multiple range test was applied to the data, the increases at the 1st, 3rd, and 5th minute were found to be different from the basal values with both doses ($P < 0.05$). Two-way ANOVA determined that this effect was significantly different from the effect of intracerebroventricular physiological saline ($P < 0.01$). When heart rate effects were evaluated, 0.5- and 1-μmol L-glutamic acid did not produce any significant change at all (Table 1).

Intracerebroventricular administration of NMDA at doses of 0.5 and 1 nmol produced elevations in mean arterial pressure (Table 1). The 1st and 3rd minute mean arterial pressure values in the 0.5-nmol group and 1st, 3rd and 5th minute mean arterial pressure values in the 1-nmol group were significantly different from the basal levels, according to Duncan's multiple range test followed by one-way ANOVA ($P < 0.05$). Intracerebroventricular injections of NMDA at doses of 0.5 and 1 nmol produced no significant change in heart rate (Table 1).

Kainic acid injected intracerebroventricularly at doses of 5 and 10 pmol caused elevations of blood pressure. Kainic acid caused statistically significant increases at the 1st and the 3rd minute, and 1st, 3rd, and 5th minute in the mean arterial pressure at doses of 5 and 10 pmol, respectively (Table 1; $P < 0.01$). A sudden decrease in the heart rate with 5- and 10-pmol doses of kainic acid started within the 1st minute and the heart rate then returned to its basal levels in 20 min. Ten-picomole kainic acid caused statistically significant decreases in heart rate within the 1st, 3rd, 5th and 10th minute (Table 1; $P < 0.05$).

3.2. Cardiovascular responses to intracerebroventricular injection of NMDA or kainic acid in APV- or DNQX-pretreated animals

Five minutes before the intracerebroventricular administration of 1 nmol of NMDA, APV microinjections were given into the paraventricular nucleus with doses 10, 25 and 50 nmol at 0 min (Fig. 2). It was shown that the microinjection of APV into the paraventricular nucleus produced no change in the time course values of mean

Table 2
Time course of heart rate (beats/min) after intracerebroventricular (i.c.v.) injection of NMDA (1 nmol) or kainic acid (KA; 10 pmol) in APV- or DNQX-pretreated animals, respectively
Values are expressed as means ± SEM. Microinjection of APV, DNQX or vehicle (2.5 β-cylodextrin) was given into the paraventricular nucleus of the hypothalamus (PVN).

Treatment	Time (min)					
	Basal	1	3	5	10	30
APV (10 nmol; PVN) + NMDA (i.c.v.)	358 ± 19	384 ± 21	385 ± 15	369 ± 13	365 ± 18	369 ± 11
APV (20 nmol; PVN) + NMDA (i.c.v.)	360 ± 4	380 ± 8	391 ± 12	382 ± 11	372.5 ± 8	359 ± 3
APV (50 nmol; PVN) + NMDA (i.c.v.)	366 ± 19	357 ± 18	375 ± 14	355 ± 15	367 ± 7	349 ± 5
Saline (PVN) + NMDA (i.c.v.)	364 ± 13	345 ± 23	373 ± 24	369 ± 26	364 ± 26	386 ± 30
DNQX (20 pmol; PVN) + KA (i.c.v.)	355 ± 6	304 ± 1[a]	282 ± 3[a]	282 ± 3[a]	300 ± 6[a]	320 ± 5
DNQX (40 pmol; PVN) + KA (i.c.v.)	362 ± 5	287 ± 14[a]	284 ± 16[a]	287 ± 14[a]	291 ± 13[a]	320 ± 22
DNQX (80 pmol; PVN) + KA (i.c.v.)	351 ± 2	279 ± 8[a]	279 ± 8[a]	286 ± 10[a]	287 ± 9[a]	316 ± 14
2.5 β-cylodextrin (PVN) + KA (i.c.v.)	351 ± 5	310 ± 6	304 ± 10	325 ± 6	340 ± 16	362 ± 16

[a] Indicates significance of differences from baseline levels using one-way ANOVA followed by the post-hoc test of Duncan, $P < 0.05$.

arterial pressure within the first 5 min when compared to time 0 values. Pretreatment with APV 5 min before administration of NMDA prevented the NMDA-evoked blood pressure changes in a dose-related manner. On the other hand, physiological saline microinjections given into the paraventricular nucleus failed to block the blood pressure responses to NMDA (Fig. 2). In the group receiving physiological saline pretreatment, NMDA produced significant elevations in mean arterial pressure within 10 min when compared to basal levels before the intracerebroventricular NMDA injections (time: 5 min) ($P < 0.01$). The arterial blood pressure responses produced by intracerebroventricular injection of 1-nmol NMDA in rats pretreated with 25- and 50-nmol APV were significantly different from those of the physiological saline-pretreated group when analyzed by two-way ANOVA ($P < 0.01$). APV pretreatment did not produce any effect on heart rate (Table 2).

Five minutes before the intracerebroventricular administration of 10 pmol of kainic acid, DNQX microinjections were given into the paraventricular nucleus with doses of 20, 40 and 80 pmol at 0 min. (Fig. 3). At these doses, DNQX did not produce significant arterial pressure and heart rate changes within the first 5 min. The vehicle, β-cyclodextrine, itself produced no statistically significant responses when injected parenchymally into the paraventricular nucleus. Analysis of the DNQX and vehicle pretreatments by two-way ANOVA showed that none of the three DNQX doses was able to antagonize the effect of intracerebroventricular kainic acid injection. The mean arterial pressure values were statistically significant in all groups compared to the 5-min values. The bradycardiac effect of intracerebroventricular kainic acid was not reversed by the DNQX pretreatment at the paraventricular nucleus (Table 2).

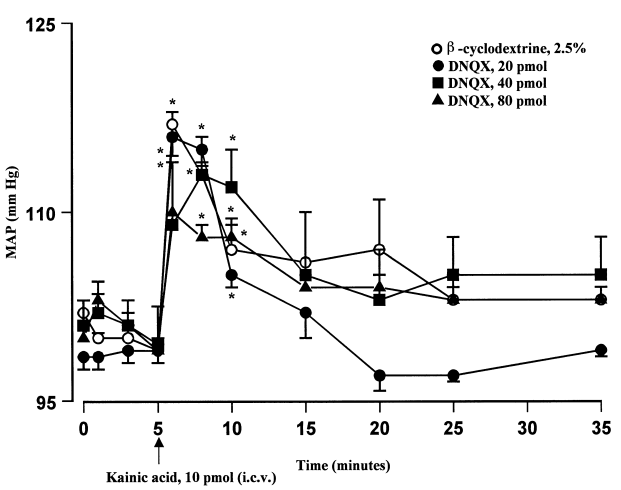

Fig. 3. Blood pressure responses to intracerebroventricular injection of kainic acid in DNQX (20, 40 and 80 pmol) or vehicle (2.5% β-cyclodextrine)-pretreated animals. Values represent means ± SEM. Asterisks indicate significance of differences from baseline levels, using one-way ANOVA followed by the post-hoc test of Duncan. * $P < 0.05$.

3.3. Cardiovascular responses to NMDA or kainic acid injected into the paraventricular nucleus of the hypothalamus

When NMDA was microinjected into the paraventricular nucleus with doses of 50 and 100 pmol, NMDA, 100 pmol, produced statistically significant changes in the time course of mean arterial pressure at the 1st, 3rd and 5th minute (Table 1). This effect was significantly different from the values of the group receiving physiological saline microinjections into the paraventricular nucleus ($P < 0.05$). No statistically significant change in heart rate was observed (Table 1).

Kainic acid, when microinjected into the paraventricular nucleus at the doses of 0.1 and 0.5 pmol, did not produce marked changes in mean arterial pressure (Table 1). Statistical analysis revealed no significant difference in either mean arterial pressure or heart rate (Table 1).

4. Discussion

Findings of this study demonstrate that intracerebroventricular administration of L-glutamic acid, NMDA or kainic acid causes significant and dose-dependent increases in mean arterial pressure. In our preliminary experiments, we tried to use the intrathecal doses reported by Hong and Henry (1992a,b) as intracerebroventricular doses for L-glutamate, NMDA and kainic acid. Since seizure activity occurred following intracerebroventricular administration of 2 nmol of NMDA in the first series of experiments, half of the presumed dose was chosen as the intracerebroventricular dose in conscious rats. It may be noted that forebrain structures require smaller doses to elicit cardiovascular effects than do spinal structures.

Experimental immunohistochemical and pharmacological studies show that the hypothalamus is one of the areas involved in the regulation of cardiovascular function and contains high levels of glutamate and ionotropic glutamate receptors (Meeker et al., 1994; Singewald and Philippu, 1996). Previous studies have shown that different nuclei of the hypothalamus, such as dorsomedial and posterior, have been recognized as having an important role in the control of autonomic and behavioral mechanisms (Waldrop et al., 1988; Stots-Potter et al., 1996). In addition to the dorsomedial and posterior nuclei of the hypothalamus, the paraventricular nucleus is also involved in cardiovascular homeostasis in rats (Martin et al., 1993). The blockade of NMDA or kainate receptors in the paraventricular nucleus by parenchymal administration of antagonists, followed by intracerebroventricular administration of NMDA or kainic acid into the lateral ventricle, would be a better approach to evaluate the participation of the group of neurons within the paraventricular nucleus of the hypothalamus and the

receptor subtypes involved in the cardiovascular effects mediated by ionotropic glutamate receptors. Microinjection of APV into the paraventricular nucleus antagonized the mean arterial pressure responses to intracerebroventricular NMDA in our study. ID_{50} was calculated using linear regression with the percent changes in the maximum responses to the intracerebroventricular NMDA injections in the rats pretreated with APV, with regard to the rats pretreated with saline. ID_{50} for APV was 12.7 nmol. On the other hand, the blockade of the kainate receptors by DNQX in the paraventricular nucleus did not alter the mean arterial pressure or heart rate effects of intracerebroventricular kainic acid. The increase in the DNQX dose would not help because of the non-specific effects of DNQX. In addition, the data for microinjections of NMDA or kainic acid into the paraventricular nucleus showed that kainate receptors in the paraventricular nucleus are not as much involved as the NMDA receptors, because microinjection of kainic acid into the paraventricular nucleus produced slight blood pressure responses. In a previous study, chemical stimulation with glutamate and kainic acid injection into the paraventricular nucleus was reported for rabbits (Tibiriça et al., 1993). These data showed that stimulation of the neuronal cell bodies of the paraventricular nucleus caused an increased sympathetic outflow to the heart, indicating an integrative role of the paraventricular nucleus involved in neural as well as humoral regulation of the cardiovascular system. In a more recent study by this group, electrical stimulation of the paraventricular nucleus in rabbits anesthetized with pentobarbital produced a positive inotropic effect, increase in blood pressure and myocardial oxygen demand, whereas administration of antagonists of different sites of NMDA receptors (intracerebroventricular injection of dichlorokynurenic acid and APV and intravenous ketamine) blunted these responses (Monassier et al., 1994). Electrical stimulation cannot be regarded as a very specific way to show the effects of the specialized group of neurons, since it also causes stimulation of the nerve fibers crossing that nucleus. Chemical stimulation is an alternative way to postulate the specific effects in that nucleus. The increase may be due to the stimulation of the neurons making synapses to the autonomic nervous system directly or indirectly or due to the humoral factors secreted from the paraventricular nucleus. It has been shown that there is a parallel relationship between the increases in blood pressure and heart rate due to stimulation of the paraventricular nucleus by L-glutamate in the rats and the increase of norepinephrine and epinephrine levels in the plasma (Martin and Haywood, 1992). All these results and our findings implicate the regulatory involvement of the ionotrophic glutamate receptors in cardiovascular homeostasis as well as in several pathophysiologic conditions such as epilepsy and dementia (Croucher et al., 1982; Dodd et al., 1984; Engelsen, 1986; Rothman and Olney, 1987; Mody and MacDonald, 1995; De Novellis et al., 1995).

Cardiovascular effects produced with microinjections of NMDA into the paraventricular nucleus were observed as strong responses similar to responses produced by the intracerebroventricular injections, but kainic acid failed to produce the same type of responses when injected parenchymally into the paraventricular nucleus. NMDA produced an increase in the heart rate that was not statistically significant. On the contrary, kainic acid injected into the paraventricular nucleus had no significant effect on the cardiovascular parameters. Several higher doses were tried but discontinued as they produced convulsions in the rats.

In conclusion, the results of this study indicate the participation of ionotropic glutamate receptors in central cardiovascular regulation and a glutamergic influence on blood pressure regulation via NMDA receptors in the paraventricular nucleus of the hypothalamus in rats.

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