Amino Acids (2003) 24: 397–403
DOI 10.1007/s00726-002-0342-4

Amino
Acids
Printed in Austria

The role of ionotropic receptors of glutaminic acid in cardiovascular system

A. The influence of ionotropic receptor NMDA agonist – 1R,3R-ACPD and antagonist – DL-AP7 on the systemic pressure in rats

E. M. Sitniewska, R. J. Wiśniewska, and **K. Wiśniewski**

Department of Pharmacology, Medical University of Białystok, Białystok, Poland

Received August 6, 2002
Accepted October 10, 2002
Published online January 20, 2003,

Summary. The aim of our study was to estimate the involvement of the peripheral N-methyl-D-aspartate receptors in regulation of cardiovascular function. For this purpose we examined the effects of intravenous injection of the agonists – NMDA (0.025; 0.05 and 1.0 mg/kg iv) and 1R-3R-ACPD (0.025; 0.05 and 1.0 mg/kg iv) – and antagonist of NMDA receptors DL-AP7 (0.02; 0.07 and 0.2 mg/kg iv). To determine if the effects of NMDA come from central or peripheral action we observed the effect during blockade of autonomic ganglion by using the nicotinic receptor antagonist – chlorisondamine (1.25 mg/kg iv). Administration of NMDA in three doses evoked slight hypotension after injection of the medium dose, 0.05 mg/kg. In the condition of pretreatment with 1.25 mg/kg chlorisondamine the hypotensive effect of NMDA was markedly reduced, what might suggest that NMDA-induced hypotension raised from the action within the brain. The competetive NMDA receptor antagonist DL-AP7 slightly increased the blood pressure. None of the injected drug had an influence on the heart rate in our *in vivo* study.
It is concluded that the peripherally localized NMDA receptors may take a part in regulation of cardiovascular system, since their stimulation or blockade evoked the changes of systemic pressure.

Key words: NMDA receptors – Systemic administration – Blood pressure – Heart rate

Introduction

The excitatory amino acids can interact with et least three subtypes of glutamate ionotropic receptors designed as kainate, N-methyl-D-aspartate (NMDA), and quisqualate. There is a well documented evidence that local application of specific antagonist of excitatory amino acids to neurons influenced the cardiovascular activity (Seagard et al., 1999; Frigero et al., 2000). These data are important because they indicate a key role for endogenous occurring excitatory amino acids at specific point in the central nervous system in controlling cardiovascular activity. However, in view of the reports that excitatory amino acids may exert a role at several synapses within a reflex neural pathway (for ref. see Guyenet et al., 1987; Collingridge and Lester, 1989; Bazil and Gordon, 1991; Colambari et al., 1994; Satoru and Sved, 1997; Satoru et al., 2000) and also in view of peripherally found the glutamate receptors (Kumar et al., 1991; Marhenn et al., 1994; Gill et al., 1999) these results cannot be sufficient to foresee the changes of cardiovascular system upon systemic administration of agonist and antagonists of ionotropic glutamate receptors.

The principal site for the integration of information regulating blood pressure is medulla oblongata (Somogyi et al., 1989). The nucleus tractus solitarii (NTS) in the dorsomedial medulla is strictly connected with ventrolateral medulla (VLM) in which neuro-transmission is influenced by excitatory amino acids (Foley et al., 1999). In some previous report microinjection of agonists and antagonists of ionotropic glutamate receptors into NTS changed the systemic blood pressure and the heart rate (Guyenet et al., 1987; Colambari et al., 1994; Wang et al., 2000). It has been reported that ionotropic and metabotropic receptors are localized not only in central nervous system (Collingridge and Lester, 1989; Scatton, 1993) but they are also found in preganglionic sympathetic

neurons, adrenal glands (Yoneda et al., 1986), spleen and cardiomyocytes (Lewis et al., 1989; Marhenn et al., 1994; Winter and Baker, 1996; Gill et al., 1999). It is not known about the role of ionotropic glutamate receptors in regulating sympathetic tone or systemic pressure and heart rate.

The first purpose of the following experiments is to find out if there are any changes in systemic pressure and the heart rate after peripheral administration of competitive agonists and antagonists of NMDA receptors. The second goal is to determine whether the cardiovascular control of NMDA receptors is their central or peripheral action.

Material and method

Animals

The experiment was carried out on male Wistar rats with body weight of 200–250 g, fed a commercial pellet diet for rodents. The animals were kept in air conditioned rooms at a constant temperature of 22°C and humidity of 60%, in darkness from 7.00 p.m. to 7.00 a.m.

Drugs

NMDA (N-Methyl-D-aspartic acid), 1R,3R-ACPD [(1R,3R)-1-Aminocyclopentane-*cis*-1,3-dicarboxylic acid], chlorisondamine diiodide, DL-AP7 (DL-2-Amino-7-phosphonoheptanoic acid) were purchased from TOCRIS. Saline, diethyl ether for narcosis, heparin were from Polfa – Warszawa, Poland.

Measurements of arterial blood pressure by direct method

The rats were anaesthetized with chloral hydrate at a dose 0.4 g/kg ip. The internal carotid artery was cannulated and direct systolic (SBP), diastolic (DBP) blood pressure were measured from right carotid artery via pressure transducer (Gould P231D). The transducer was connected to the monitor Trendoscope 8031 (Unitra Biazet S&W Medico Teknic, A/S Denmark). The changes in systolic and diastolic blood pressure were recorded in mmHg. The heart rate (HR) was recorded with EKG (beats/min). The vagal nerve was sectioned bilaterally to exclude influence of cholinergic fibres on the action of the examined substances. The left femoral vein was cannulated for iv administration of drugs in a volume 0.1 ml. After 10 minutes of equilibration parameters were allowed to stabilize and the experiments were performed. The SBP of the control group ($n = 8$) was 97.0 mmHg $\pm$ 6.56, DBP – 74.5 mmHg $\pm$ 2.3, heart rate (HR) was 408 beats/min $\pm$ 19.3. Through the whole experiment lasted 2.5 hours the systemic pressure did not significantly changed.

Experimental protocol

NMDA was injected as a bolus dose of 0.025; 0.05; 1.0 mg/kg iv into the femoral vein to which free access were prepared at the beginning of the experiment. The whole experiment after injection of each substance lasted 150 min. After administration of each drug the values of the SBP, DBP and HR were registered every minute for the first thirty minutes and than every 5 minute to the end of the experiment.

(1R,3R)-ACPD, potent specific NMDA receptor agonist was administered as a bolus of 0.025; 0.05; 1.0 mg/kg iv, in doses equimolar to NMDA.

DL-AP7, specific NMDA receptor antagonist, was given as a bolus of 0.02; 0.07; 0.2 mg/kg and ion channel site modulator, MK-801 was injected in equimolar to DL-AP7 doses (0.03; 0.1; 0.3 mg/kg iv).

To test if the effect of DL-AP7 is reversible by NMDA-receptor agonist we examined the changes in SBP, DBP and HR during combined administration of both substances. 15 min before the injection of 0.05 mg/kg of NMDA the dose of 0.2 mg/kg of DL-AP7 was administered.

In order to check whether the action of NMDA is its peripheral or central effect we examined the changes during blockade of central nicotinic receptors induced by long lasting nicotinic antagonist – chlorisondamine (1.25 mg/kg). It was administered 15 min before the injection of NMDA.

The control group received 0.1 ml 0.9% NaCl.

Statistics

The results were statistically analyzed by the analysis of variance modified by Bonferroni and Student's *t*-test for paired data. Mean values (χ), the standard errors of mean (SEM) and number of measurements in the group (n) are presented in the figures (Wallenstein et al., 1980).

Results

NMDA given in three doses evoked tendency to decrease SBP, DBP and HR. The smallest dose did not influence the systemic pressure and heart rate. The medium dose significantly decreased SBP and DBP in 20th and 30th minute and presented biphasic effect on the systemic pressure with the recovery to the initial values after the first 45 minutes of the experiment. During the last 30 min it evoked tendency to decrease SBP. The highest dose of NMDA caused not significant ($p > 0.05$) decrease of SBP, DBP and HR (Fig. 1).

Chlorisondamine evoked deep and stabile decrease in SBP, DBP and HR, which was maintained through the whole 150 min of experiment. Combined administration of NMDA (0.05 mg/kg) and chlorisondamine abolished the slight tendency to decrease systemic pressure by NMDA and also attenuated deep and prolonged hypotension caused by ganglion blockade (Fig. 2).

1R,3R-ACPD, potent, non selective NMDA receptor agonist, given at three equimolar to NMDA doses, did not markedly influence the systemic pressure and a heart rate. Contrary to NMDA, it slightly increased the SBP and DBP, but the values were not significant neither to the control group nor to NMDA (Fig. 3).

DL-AP7, first generation phosphono NMDA antagonist was administered in three doses 0.02, 0.07

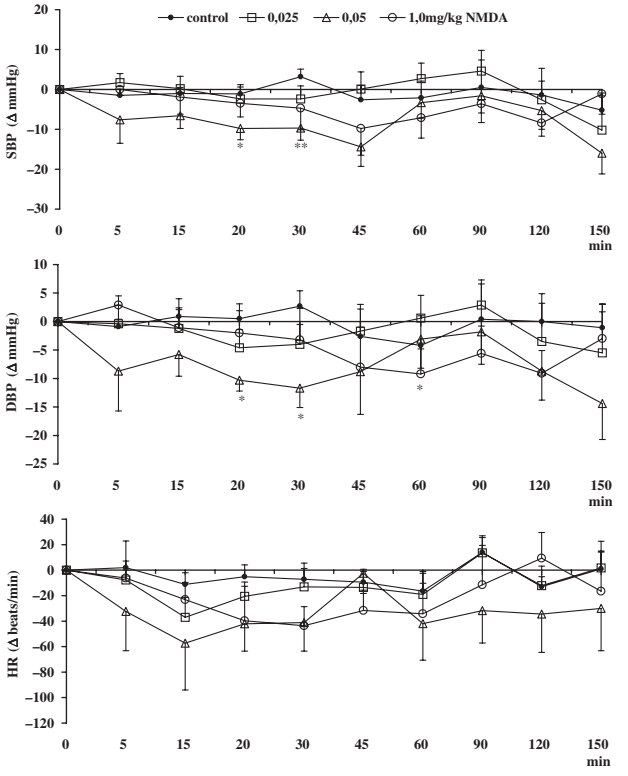

Fig. 1. Effect of NMDA (0.025; 0.05 and 1.0 mg/kg iv) on systolic (*SBP*), diastolic blood pressure (*DBP*) and heart rate (*HR*). * $p < 0.05$; ** $p < 0.01$ vs control group (n = 6)

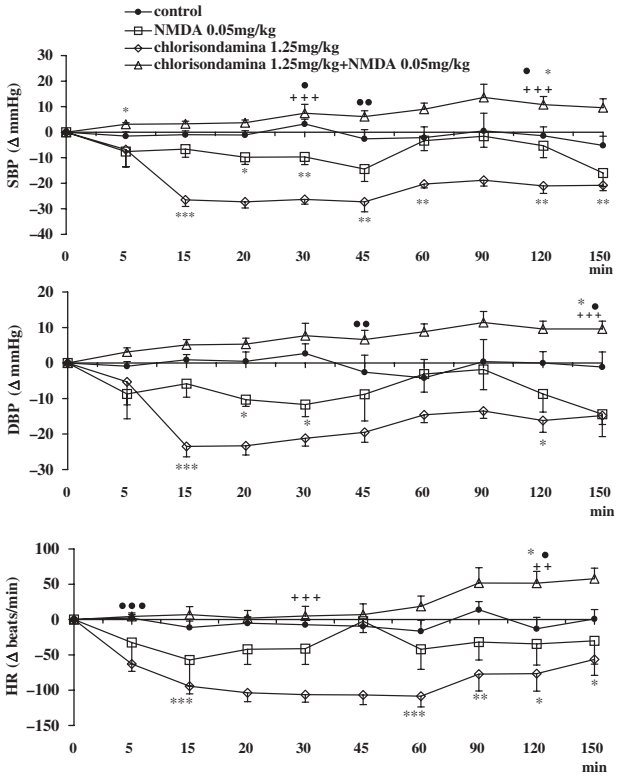

Fig. 2. Effect of combined administration of NMDA (0.05 mg/kg iv) and chlorisondamine (1.25 mg/kg iv) on systolic (*SBP*), diastolic blood pressure (*DBP*) and heart rate (*HR*) (n = 6). * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs control group $^{++}p < 0.01$, $^{+++}p < 0.001$ vs chlorisondamine; $^{\bullet}p < 0.05$; $^{\bullet\bullet}p < 0.01$; $^{\bullet\bullet\bullet}p < 0.001$ vs NMDA

and 0.2 mg/kg. The smallest dose of the NMDA receptor antagonist did not significantly change the systemic pressure or the heart rate. The medium dose of DL-AP7 decreased the heart rate ($p < 0.05$ vs control group in 150th min). The highest dose (0.2 mg/kg iv) increased the systemic pressure. The effect was observed since the beginning of the experiment and slowly grew up until the 120th minute. In the 20th, 60th and 120th minutes the values of SBP and DBP were significant ($p < 0.05$) vs control group (Fig. 4).

Combined administration of DL-AP7 (0.2 mg/kg) and NMDA (0.05 mg/kg, given in 15th min of DL-AP7 infusion) evoked in the 16th min the decrease of SBP ($p < 0.01$ vs control) and DBP ($p < 0.01$ vs control and $p < 0.05$ vs NMDA) with no any changes in HR (Fig. 5).

Discussion

The NMDA receptor subtype is distinguished from other glutamate-gated ion channels receptors by number of selective agonists and antagonists and also by specific properties including high Ca^{2+} permeability, modulation by glycine, voltage-dependent Mg^{2+} blockade and inhibition by Zn^{2+} and several selective open channel blockers (Monaghan et al., 1989). Several subunits of NMDA receptor (NMDAR1, NMDAR2A-NMDAR2D) were described (Monyer et al., 1992; Ishii et al., 1993). Kumar et al. (1991) found NMDAR1 receptor in brain and heart cells and absent in liver, lung and muscle. This subunit was already cloned (Ishii et al., 1993; Gill et al., 1998) and it was also determined as an essential for the function of the whole NMDA receptor. The other subunits potentiate and differentiate the function by forming different heteromeric configurations with NMDAR1 (Ishii et al., 1993; Marhenn et al., 1994).

In the previous experiments we examined the influence of the injection as a bolus dose of 0.03, 0.1 and 0.3 mg/kg iv of MK-801, a potent selective and noncompetetive NMDA receptor antagonist on SBP, DBP and HR. MK-801 administered in the lowest dose of 0.03 mg/kg did not significantly change the systemic pressure or heart rate. MK-801 given in the

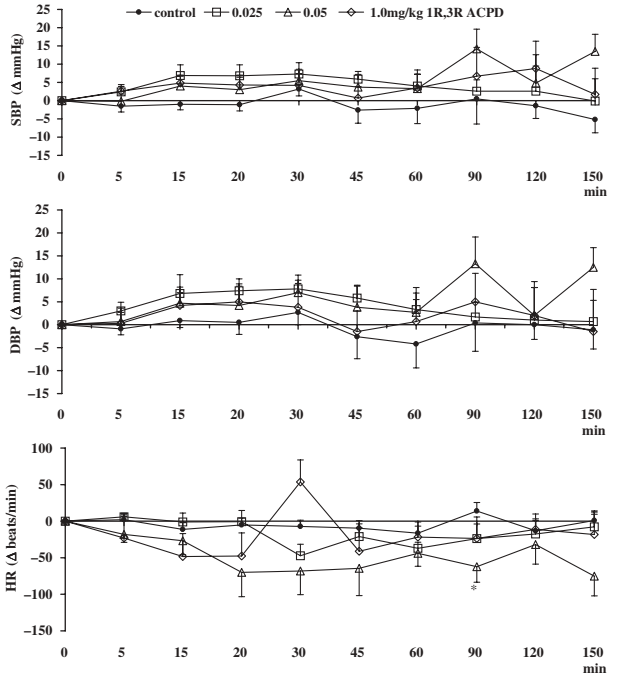

Fig. 3. Effect of 1R,3R ACPD (0.025; 0.05 and 1.0 mg/kg iv) on systolic (*SBP*), diastolic blood pressure (*DBP*) and heart rate (*HR*) (n = 6). * $p < 0.05$ vs control group

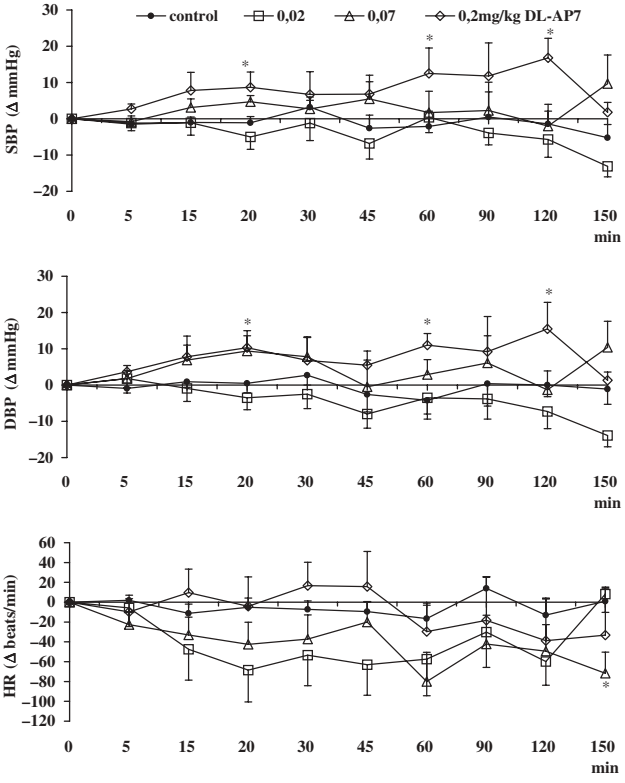

Fig. 4. Effect of DL-AP7 (0.02; 0.07 and 0.2 mg/kg iv) on systolic (*SBP*), diastolic blood pressure (*DBP*) and heart rate (*HR*) (n = 6). * $p < 0.05$ vs control group

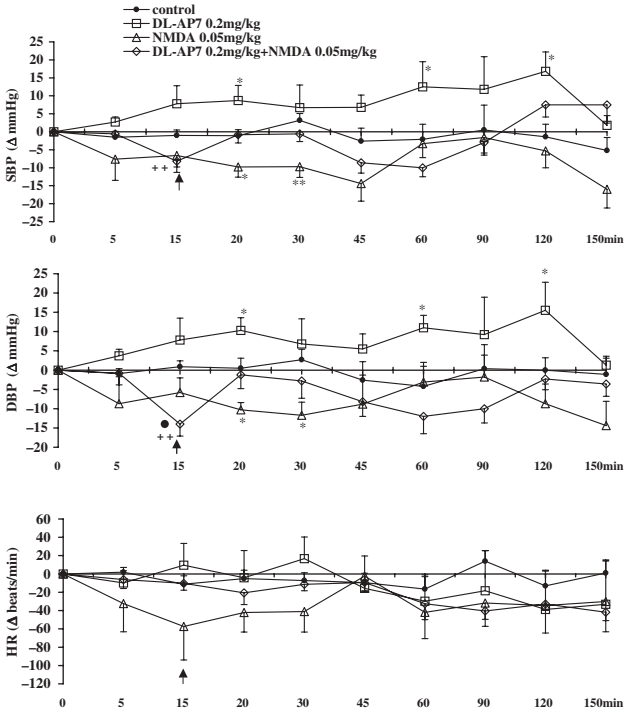

Fig. 5. Effect of combined administration of NMDA (0.05 mg/kg iv) and DL-AP7 (0.2 mg/kg iv) on systolic (*SBP*), diastolic blood pressure (*DBP*) and heart rate (*HR*) (n = 6). * $p < 0.05$, ** $p < 0.01$ vs control group $^{++}$ $p < 0.01$ vs DL-AP7; • $p < 0.05$ vs NMDA

medium dose of 0.1 mg/kg iv slightly increased SBP and DBP. The values were significant in 20 min after administration of antagonist ($p < 0.01$ in SBP and $p < 0.05$ in DBP vs control). Hypertensive effect of the highest dose (0.3 mg/kg) started from the beginning of the test and it was maintained through the almost whole time of experiment. The increase systemic pressure was significant both in SBP and DBP, especially in the first hour of examination ($p < 0.01$ and $p < 0.05$ vs control respectively SBP and DBP). None of the doses of MK-801 influenced the heart rate (Wiśniewska et al., 2000). Our results of the MK-801 induced changes of arterial blood pressure are consistent with other reports (Lewis et al., 1989; Abrahams et al., 1993). Contrary to tachycardia noted by Lewis et al. (1989), our data confirmed the lack of the MK-801 influence on the heart rate observed by Abrahams et al. (1993). Stevens and Yaksh (1990) reported the significant increase of systemic pressure of bolus dose 0.1 mg/kg with no further increase observed at higher doses (0.5; 1.0; 2.0 mg/kg iv).

In the present study we noted that activation the glutaminergic ionotropic receptors by specific agonist NMDA, given intravenously, evoked slight

hypotension with no influence on the heart rate. We tested three doses of NMDA, but the only medium one (0.05 mg/kg) had a slight hypotensive effect ($p < 0.05$ vs control). Because the glutaminergic ionotropic receptors are found not only in CNS, but they are also localized in the heart – especially NMDAR1 and Ka2 (Marhenn et al., 1994; Gill et al., 1999), the question not answered yet is if the slightly hypotensive effect of NMDA was the result of activation of central or rather peripheral receptors. To get an answer we observed the effect of 0.05 mg/kg NMDA during long lasting blockade of nicotinic receptors by chlorisondamine. 1.25 mg/kg of chlorisondamine evoked deep decreased SBP ($p < 0.001$ vs control), DBP ($p < 0.001$ vs control) and bradycardia ($p < 0.001$), what was maintained through the whole experiment. Consistent with the bisquaternary structure, chlorisondamine does not appear to penetrate the central nervous system. The effect of chlorisondamine observed in our experiment after systemic administration raised from temporary peripheral ganglion nicotinic receptors blockade (Clarke et al., 1994; El-Bizri and Clarke, 1994).

NMDA, as a principal agonist of ionotropic receptors activates the receptor complex by combining with the "transmitter recognition site" which, via a linkage mechanism, transforms the ion channel to an open state allowing the conductance of Na^+, Ca^{2+}, and K^+ ions to initiate the neuronal response. The heart distribution of NMDAR1 receptor was wider than other subtype of ionotropic glutamate receptors, which were preferentially found in cardiac nerve terminals, ganglia cells, conducting fibres and also in myocardiocytes particularly of atrium (Gill et al., 1998). Rockhold et al. (1989) indicated that NMDA administrated into paraventricular hypothalamus of rats produced increased arterial blood pressure and heart rate, pretreatment with labetalol reduced studied effect. They suggested that cardiotoxicity de-pend on release catecholamines mainly in endocardial regions of left ventricle. NMDA administered in dose 10-fold higher (37 μg/kg iv) had no effect on systemic cardiovascular changes (Rockhold et al., 1989). There are some previous reports that central administration of L-glutamate (Haibara et al., 1999) or NMDA (Machado et al., 2000) produces hypotensive and bradycardic response. It was already observed that that central administration of NMDA receptor agonists elevated while antagonists decreased blood pressure (Bazil and Gordon, 1991; Gordon, 1995).

In our experiment noncompetitive, centrally acting NMDA receptor antagonist MK-801, which readily penetrates into the central nervous system (Hucker, 1982; Wong et al., 1986; Hargreaves and Cain, 1992) slightly, increased SBP and DBP and did not changed HR. These results are probably due to central blockade of NMDA receptors (Wong et al., 1986) rather than inhibition of baroreflex, because Lewis et al. (1989) report that either ganglion blockade or adrenergic blockade attenuated the hypertension and tachycardia induced by MK-801. They also noticed that cardiovascular changes of peripheral administrated MK-801 correlated with increased renal sympathetic nerve activity. Our results are in agree with Roussel et al. (1992) and Loubinoux et al. (1994). MK-801 blocks depolarizing responses to NMDA, but its action on NMDA receptor is dependent upon NMDA receptor activation. Kemp et al. (1987) noticed that block of NMDA responses only occurred following repeated applications of NMDA, even prolonged exposure to MK-801, so it requires the activation of NMDA receptor before blocking effects can occur (Heale and Harley, 1990). MK-801 act upon the ion channel. It binds to sites within the channel that are separate from those for divalent cations when the channel is in open state, preventing the passage of ions (Kemp et al., 1987). It has been demonstrated by Uematsu et al. (1991) that intravenously administered MK-801 was able to block Ca^{++} entry during excessive activation of the NMDA receptors. The behavioral effects of MK-801 lasts for 3 hours suggesting the strong influence of this antagonist on NMDA receptor (Hargreaves and Cain, 1995).

The competitive antagonist of NMDA receptor, DL-AP7 injected in the highest dose 0.2 mg/kg slightly increased the SBP ($p < 0.05$ vs control in 120 min) and DBP ($p < 0.05$ vs control in 60 and 120 min) and had no influence on HR. Combined injection of both substances attenuated their actions, either slight hypertensive of 0.2 mg/kg DL-AP7 or slight hypotensive of 0.05 mg/kg NMDA. As a competitive receptor antagonist mechanism of action of DL-AP7 consists of (Kemp et al., 1987) prevention receptor activation by competing with agonist for the transmitter recognition site. Feldman and Buccafusco (1997) noticed slight decrease resting blood pressure and heart rate in conscious rats. They also examined DL-AP7 influence on intrathecal (it) injection of muscarinic receptor agonist carbachol. The intrathecal pretreatment with D-AP7 or MK-801 attenuated the

pressor response to intrathecal administration of carbachol while the intravenous administration of D-AP7 was without effect on cardiovascular response to central injection of carbachol. These results suggest that in regulation of vascular tonic activity and the heart rate the glutaminregic and spinal muscarinic receptor system strongly participate and that DL-AP7 poorly penetrates into the brain (Feldman and Buccafusco, 1997).

Competitive agonist of NMDA receptor, 1R,3R-ACPD had no significant cardiovascular effect in our *in vivo* experiment. All three doses (0.025; 0.05 and 1.0 mg/kg) evoked slight but significant tendency to increase the SBP and DBP and to decrease HR. According to Mistry and Challiss (1996) this agonist acts indirectly on phosphoinositide responses through activation of NMDA-type ionotropic glutamate receptors because the response to 1R,3R ACPD was largely prevented by pre-addition of the NMDA-receptor antagonist, MK-801, or omission of extracellular Ca^{++}. They noticed a rapid and substantial increase in $Ins(1,4,5)P_3$ accumulation after 1R,3R-ACPD injection. In a presence of MK-801 a small component of this response was still apparent, what can suggest that 1R,3R-ACPD might be a partial agonist at mGluR or cause a small $Ins(1,4,5)P_3$ response via another undefined mechanism.

In summary, intravenous administration of NMDA evoked slightly hypotensive effect. The small cardiovascular response after administration of DL-AP7 and 1R,3R-ACPD may reflect their poor penetration into the brain, not specific receptor action or other not known yet mechanism of action. Our results indicate that intravenous administration of both the agonist and antagonist evoked changes in systematic pressure. These data suggest that peripherally localized NMDA receptors might play a role in regulating cardiovascular function. In the view of findings of strong distribution of several isoform of excitatory amino acid receptors (GluR2/3, GluR5/6/7, Ka2 and NMDAR1) in the rat heart the further investigation on isolated heart needs to be done to elucidate the role of glutamate receptors in regulation of cardiovascular function.

Aknowledgments

This study was supported by a grant No 3-10871 from the State Committee for Scientific Research, Warszawa, Poland. The authors thank Ms. A. Barwińska and Ł. Stalenczyk for technical help.

References

Abrahams TP, DeSilva AMT, Hamosh P, McManigle JE, Gillis RA (1993) Cardiorespiratory effects produced by blockade of excitatory amino acid receptors in cats. Eur J Pharm 238: 223–233

Bazil MK, Gordon FJ (1991) Spinal NMDA receptors mediate pressor responses evoked from the rostral ventrolateral medulla. Am J Physiol 260: H267–H275

Clarke PBS, Chaudieu I, El-Bizri H, Boksa P, Quik M, Esplin BA, Capek R (1994) The pharmacology of the nicotinic antagonist, chlorisondamine, investigated in rat brain and autonomic ganglion. Br J Pharmacol 111: 397–405

Colambari E, Bonagamba LGH, Machado BH (1994) Mechanism of pressor and bradycardic responses to L-glutamate microinjected into the NTS of conscious rats. Am J Physiol 266: R730–R738

Collingridge GL, Lester RAJ (1989) Excitatory amino acids receptors in the vertebrate central nervous system. Pharmacol Rev 40: 143–210

El-Bizri H, Clarke PBS (1994) Regulation of nicotinic receptors in rat brain following quasi-irreversible nicotinic blockade by chlorisondamine and chronic treatment with nicotine. Br J Pharmacol 113: 917–925

Feldman DS, Buccafusco JJ (1997) Spinal muscarinic, glutamergic and GABAergic receptor systems in cardiovascular regulation. J Pharmacol Exp Ther 281: 274–283

Foley CM, Vogl HW, Mueller PJ, Hay M, Hasser EM (1999) Cardiovascular response to group I metabotropic glutamate receptor activation in NTS. Am J Physiol 276: R1469–R1478

Frigero M, Bonagamba LG, Machado BH (2000) The gain of the baroreflex bradycardia is reduced by microinjection of NMDA receptor antagonists into the nucleus tractus solitarii of awake rats. J Auton Nerv Syst 79 1: 28–33

Gill SS, Pulido OM, Mueller RW, McGuire PF (1998) Molecular and immunochemical characterization of the ionotropic glutamate receptors in the rat heart. Brain Res Bull 46: 429–434

Gill SS, Pulido OM, Mueller RW, McGuire PF (1999) Immunochemical localization of the metabotropic glutamate receptors in the rat heart. Brain Res Bull 48: 143–146

Gordon FJ (1995) Excitatory amino acid receptors in central cardiovascular regulation. Clin Exp Hypertens 17/1–2: 81–90

Guyenet PG, Filtz TM, Donaldson SR (1987) Role of excitatory am2ino acids in rat vagal and sympathetic baroreflex. Brain Res 407: 272–284

Haibara AS, Bonagamba LGH, Machado BH (1999) Sympatho-excitatory neurotransmission of the chemoreflex in the NTS of awake rats. Am J Physiol 276: R69–R80

Hargreaves EL, Cain DP (1992) Hyperactivity, hyper-reactivity, and sensorimotor deficits induced by low doses of the N-methyl-D-aspartate non competitive channel blocker MK-801. Behav Brain Res 47: 23–33

Hargreaves EL, Cain DP (1995) MK-801-Induced Hyperactivity: duration of effects in rats. Pharmacol Biochem Behav 51: 13–19

Heale V, Harley C (1990) MK801 and AP5 impair acquisition but not retention of the Morris milk maze. Pharmacol Biochem Behav 36: 145–149

Hucker HB, Hutt JE, Zacchei AG, Arison BH (1982) Disposition and metabolism of (+)-5-methyl-10,11-dihydro-5H-dibenzo[a,d] cyclohepten-5,10-imine (MK-801). Fed Proc Abst 8554

Ishii T, Moriyoshi K, Sugihara H, Sakurada K, Kadotani H, Yokoi M, Akazawa Ch, Shigemoto R, Mizuno N, Masu M, Nakanishi S (1993) Molecular characterization of the family of the N-methyl-D-aspartate receptor subunits. J Biol Chem 268: 2836–2843

Kemp JA, Foster AC, Wong EHF (1987) Non-competetive antagonists of excitatory amino acid receptors. TINS 10: 294–298

Kumar KN, Tilakaratne N, Johnson PS, Alen AE, Michaelis EK (1991) Cloning of cDNA for glutamate-binding subunit of on NMDA receptor complex. Nature 354: 70–73

Lewis SJ, Barres Ch, Jackob HJ, Ohta H, Brody M (1989) Cardiovascular effects of the N-Methyl-D-Aspartate receptor antagonist MK-801 in conscious rats. Hypertension 13: 759–765

Loubinoux I, Meric P, Borredon J, Correze JL, Gillet B, Beloeil JC, Tiffon B, Mispelter J, Lhoste JM, Jacques S (1994) Cerebral metabolic changes induced by MK-801: a 1D (phosphorus and proton) and 2D (proton) in vivo NMR spectroscopy study. Brain Res 643/1–2: 115–124

Machado BH, Castania JA, Bonagamba LGH, Salgado HC (2000) Neurotransmission of autonomic components of aortic baroreceptor afferents in the NTS of awake rats. Am J Physiol Heart Circ Physiol 279: H67–H75

Mistry R, Challiss RAJ (1996) Differences in agonis and antagonis activities for two indicies of metabotropic glutamate receptor-stimulated phosphoinositide turnover. Br J Pharmacol 117: 1735–11743

Marhenn VB, Waleh NS, Mansbridge JN, Unsan D, Zolotorev A, Cline P, Tolk L (1994) Evidence for on NMDA receptor subunit in human keratinocenter and rat cardiocytes. Eur J Pharm 268: 409–411

Monaghan DT, Bridges RJ, Cotman CW (1989) The excittatory amino acid receptors: their classes, pharmacology, and distinct properties in the function of the central nervous system. Ann Rev Pharmacol Toxicol 29: 365–402

Monyer H, Sprengel R, Schoepfer R, Herb A, Higuchi M, Lomeli H, Burnshev N, Saakmann B, Seeburg PH (1992) Heteromeric NMDA receptors: molecular and functional distinction of subtypes. Science 256: 1217–1221

Rockhold RW, Acuff CG, Clower BR (1989) Excitotoxin-induced myocardial necrosis. Eur J Pharmacol 166: 571–576

Roussel S, Pinard E, Seulaz J (1992) The acute effects of MK-801 on cerebral blood flow and tissue partial pressures of oxygen and carbon dioxide in conscious and alpha-chlorase anaesthetized rats. Neuroscience 47: 958–965

Satoru I, Sved AF (1997) Tonic glutamate-mediated control of rostral ventrolateral medulla and sympathetic vasomotor tone. Am J Physiol 273: R487–R494

Satoru I, Komatsu K, Tsukamoto K, Sved AF (2000) Excitatory amino acids in the rostral ventrolateral medulla support blood pressure in spontaneously hypertensive rats. Hypertension 35: 413–417

Scatton B (1993) The NMDA receptor complex. Fundam Clin Pharmacol 7: 389–400

Seagard JL, Dean C, Hopp FA (1999) Role of glutamate receptors in transmission of vagal cardiac input to neurones in the nucleus tractus solitarii in dogs. J Physiol 520: 243–253

Somogyi P, Minson JB, Morilak D, Llewellyn-Smith I, McLlhinney JRA, Chalmers J (1989) Evidence for an excitatory amino acid pathway in the brainstem and for its involvement in cardio-vascular control. Brain Res 496: 401–407

Stevens MK, Yaksh TL (1990) Systematic studies on the effects of the NMDA receptor antagonist MK-801 on cerebral blood flow and responsivity, EEG, and blood-brain barrier following complete reversible cerebral ischemia. J Cerebral Blood Flow Metab 10: 77–88

Uematsu D, Greenberg JH, Araki N, Reivich M (1991) Mechanism underlying protective effect of MK-801 agonist NMDA-induced neuronal injury in vivo. J Cerebral Blood Flow Metab 11: 779–785

Wallenstein S, Zucker C, Fleis JL (1980) Some statistical methods useful in circulation research. Circ Res 47: 1–9

Wang JJ, Rong WF, Wang WZ, Zhang L, Yuan WJ (2000) NMDA receptor mechanism involved in arterial baroreflex. Acta Pharmacol Sin 21 7: 617–622

Winter CR, Baker RC (1996) Glutamate-induced changes in intracellular calcium oscillation frequency through non-classical glutamate receptor binding in cultured rat myocardial cells. Life Sciences 57: 1925–1934

Wiśniewska RJ, Sitniewska EM, Wiśniewski K (2000) Cardiovascular effects of the N-methyl-D-Aspartate receptor agonist and antagonist in rats. Eur Neuropsychopharmacol 10 [Suppl]: 9

Wong EHF, Kemp JA, Pristley T, Knight AR, Woodruff GN, Iversen LL (1986) The anticonvulsant MK-801 is a potent N-methyl-D-aspartate antagonist. Proc Natl Acad Sci 83: 7104–7108

Yoneda Y, Ogita K (1986) Localization of [^{3}H] glutamate binding sites in rat adrenal medulla. Brain Res 383: 387–391

Authors' address: Prof. Konstanty Wiśniewski, Department of Pharmacology, Medical University of Białystok, Mickiewicza 2c, PL-15-222 Białystok, Poland