J Neural Transm (2009) 116:551–557
DOI 10.1007/s00702-009-0217-x

Alpha and beta noradrenergic mediation of NMDA glutamatergic effects on lordosis behaviour and plasmatic LH concentrations in the primed female rat

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Received: 31 December 2008 / Accepted: 17 March 2009 / Published online: 24 April 2009

Abstract In previous studies we have found that blockade of NMDA (*N*-Methyl-D-Aspartic-Acid)-type glutamatergic receptor with intracerebroventricular (ICV) selective drugs induces an inhibition of lordosis in ovariectomized (OVX) estrogen primed rats receiving progesterone or luteinizing hormone releasing hormone (LHRH). By the opposite way, stimulation with NMDA in OVX estrogen primed rats induced a significant increase of lordosis. In the present study the action of an α1-noradrenergic antagonist, HEAT (BE 2254/2-beta-4-Hydroxyphenyl-Ethyl-Aminomethyl-1-Tetralone), and Metoprolol, a β-noradrenergic antagonist, were studied injecting them ICV previously to NMDA administration in treated OVX estrogen primed rats. In experiment 1, the enhancing effect on lordosis induced by NMDA at high dose (1 μg) was abolished by HEAT administration ($P < 0.001$ for 3 and 6 μg), and the LH plasma levels were decreased only with the higher dose ($P < 0.05$), suggesting that behavioral effects are quite more sensitive to the α-blockade than hormonal effects. In experiment 2, enhancing effects on lordosis behavior were not observed with neither the NMDA at low dose (0.5 μg) nor the metoprolol alone (5.71 μg), but a synergism was observed when both were simultaneously administered ($P < 0.001$). The LH plasma levels were increased by Metoprolol alone ($P < 0.05$), and powered by the combination with NMDA at low dose ($P < 0.01$ vs. SAL and NMDA alone); no differences were observed with Metoprolol. LH increase was observed with Metoprolol even without behavioural modifications. These findings strongly suggest that facilitatory and inhibitory effects of NMDA in this model are mediated by α- and β-adrenergic transmission in both, behavioral and hormonal effects.

Keywords Lordosis · Behavior · Glutamate · Plasmatic · LH · Noradrenergic transmission

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Introduction

Glutamic acid (GLU) and gamma-amino butyric acid (GABA) are the main amino acid transmitters of the mammalian brain, mediating, respectively, excitatory and inhibitory events (Gargiulo et al. 1992). Excitatory amino acid receptors have been divided in two broad groups

named ionotropic and metabotropic receptors (Brann and Mahesh 1994). Ionotropic receptors are divided into NMDA (*N*-methyl-D-aspartate), kainate, and AMPA (DL-alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) receptors. These types of receptors exert their actions by modulation of Na^+, K^+, and Ca^{2+} ion channels. Metabotropic receptors act by a G-protein-stimulated release of intracellular Ca^{2+} or modulation of adenylate cyclase activity (Brann and Mahesh 1994).

Low subcutaneous doses of NMDA increase luteinizing hormone in male rats (Schainker and Cicero 1980). We have previously studied the behavioral and endocrine effects of ionotropic *N*-methyl-D-aspartic acid (NMDA) and non-NMDA receptor blockades (Gargiulo et al. 1992; Gargiulo and Donoso 1995) in female rats. In these studies we have found that the activation of lordosis behavior induced by progesterone and a peptide with wide brain distribution (Samson et al. 1980), luteinizing hormone-releasing hormone (LHRH), in ovariectomized estrogen primed rats, can be blocked by the intracerebroventricular (ICV) administration of 7-amino-phosphonoheptanoic acid (AP-7), a NMDA-glutamatergic blocker (Gargiulo et al. 1992). By the opposite way, the *N*-Methyl-D-Aspartic acid, when given ICV to OVX estrogen primed rats induces an increase of plasmatic LH and lordosis behavior (Gargiulo and Donoso 1995). The first effect appears to be mediated by LHRH, since the previous ICV administration of a selective antagonist of LHRH blunted the peak of LH induced by NMDA (Gargiulo and Donoso 1995). The behavioral effect appears not to be mediated through LHRH because the selective LHRH did not affect the lordosis/mount ratio (L/M), but this effect is antagonized by the previous administration of AP-7 (Gargiulo and Donoso 1995).

All these evidences and previous findings suggest that some neurotransmitters could be interacting with glutamate aiming to produce the behavioral and endocrine effects. Catecholaminergic (Ahlenius 1993; Etgen et al. 1992) and serotoninergic transmissions (Ahlenius 1993; Gorzalka et al. 1990; Johnson and Crowley 1986; Mendelson 1992) have been implicated in mating behavior. The release of noradrenaline by glutamate has been reported (Donoso et al. 1994; Navarro et al. 1994, 1995). NMDA stimulatory actions appear to have a close hormone dependency (Gargiulo and Donoso 1995), and estradiol appears to regulate the number of α-1 but not β or α-2 noradrenergic receptors in hypothalamus of female rats (Etgen and Karkanias 1990). The blockade of LH secretion by α-1 adrenergic receptor blockade has been described (Lee et al. 1997), and brainstem catecholaminergic neurons are activated by mating in the female rat (Yang and Voogt 2001). The role of α-1-adrenoreceptors mediating facilitatory effects of the catecholamine neurotransmitter norepinephrine on both lordosis behavior and LH release has been extensively postulated (Etgen 2003). In a previous study, we have observed that prazosin, a specific non-selective α-adrenergic antagonist, decrease the lordosis behavior and luteinizing hormone secretion in the estrogen primed female rat (Landa et al. 2006). Aiming to study the possible α-1 and β-adrenoreceptor mediation of NMDA effects we used two antagonists. The α-1-adrenergic antagonist was HEAT (BE 2254/2-beta-4-hydroxyphenyl-ethylaminoethyl-1-tetralone), that has selective action on these receptors (Williams et al. 1978). The β-antagonist selected for this study was metoprolol.

The aim of the present experiment was to study the interaction between glutamatergic and noradrenergic transmission in this model. Sexual behavior was correlated with luteinizing hormone (LH) release in the same experimental animals, as it was done in our previous studies (Gargiulo et al. 1992; Gargiulo and Donoso 1995; Landa et al. 2006).

Materials and methods

Subjects

Sprague-Dawley female rats (240–270 g) were ovariectomized under ether anesthesia and kept in a reverse light cycle (lights on 19.00–7.00 h) and temperature controlled (22 ± 2°C) room. Animals were allowed access to food and water ad lib. Two weeks prior to the experiments, receptivity of the rats was assayed. Animals were injected with 20 μg estradiol benzoate (EB) SC, 48 h before, and 1 mg progesterone SC, 4 h before testing. Mating tests were conducted in a rectangular arena illuminated by a red light during the dark period, in the morning (08.00–10.00 h). Two stud males (300–400 g) were introduced into the arena at least 10 min before the female was placed. As in previous studies (Landa et al. 2006), the behavioral tests ended when the test female had received 30 male copulatory acts or after 15 min.

The Lordosis/Mount (L/M) ratio was calculated for each rat. Only responsive rats with a L/M of 80% (criterion of inclusion) in previous tests were stereotaxically implanted with a 23-gauge stainless steel guide cannulae into the 3rd brain ventricle under ether anesthesia. Coordinates for cannulae implantation were: A–C: Bregma; V: 8.5 mm; Lateral: Midline. Localization of the cannula was confirmed when CSF flowed from the cannula after the removal of an inner stylet used to prevent such leakage. The cannulae were cemented to the skull. After surgery, the animals were housed individually and maintained undisturbed for recovery. Drugs were injected intraventricularly (IVT) through a 30-gauge stainless steel tube fitted into the guide cannulae and connected to a 10 μl Hamilton microliter syringe with a polyethylene catheter. In all cases,

a volume of 2 µl solution was delivered over a period of 2 min. During IVT injections, animals were manually restrained. Each animal was tested only one time.

Experiments

In experiment 1 the effect of HEAT, an α1-noradrenergic antagonist on lordosis behavior induced by NMDA was studied. Rats implanted with IVT guide cannulae received a SC injection of 20 µg estradiol benzoate in 0.2 ml corn oil. They were injected 48 h later with saline solution (SAL, two 2 µl injections), SAL (2 µl) and NMDA (1 µg/2 µl), HEAT hydrochloride (BE 2254/2-beta-4-hydroxyphenyl-ethylaminoethyl-1-tetralone, 3 and 6 µg/2 µl) and NMDA (1 µg/2 µl) and tested for lordosis behavior 1.5 h later. In all cases, both injections were separated by a 10 min period. In each mating session, rats injected with drugs and controls were simultaneously tested.

In experiment 2 the effect of metoprolol, a β-noradrenergic antagonist on lordosis behavior induced by NMDA was studied. NMDA was used here at a low dose (0.5 µg/2 µl). Rats implanted with IVT guide cannulae received a SC injection of 20 µg estradiol benzoate in 0.2 ml corn oil. They were injected 48 h later with saline (2 µl) and NMDA (0.5 µg/2 µl), metoprolol (5.71 µg/2 µl) and saline (2 µl), and metoprolol (5.71 µg/2 µl) and NMDA (0.5 µg/2 µl). They were tested for lordosis behavior 1.5 h later. In all cases, both injections were separated by a 10 min period. In each mating session, rats injected with drugs and controls (SAL-SAL) were simultaneously tested.

In both experiments, lordosis behavior was evaluated 1.5 h after administration of the drugs. To determine copulatory LH release, rats were sacrificed by decapitation immediately after completion of lordosis tests, and blood from the trunk was collected. Plasma was separated and stored frozen until assay, frozen at −70°, waiting the end of experiments to determine luteinizing hormone (LH) levels. They were processed by Radio-Immuno-Analysis. LH was measured with a double antibody radioimmunoassay performed with materials and according to the instructions of the kits provided by the National Hormone & Pituitary Program (Harbor-UCLA Medical Center, Torrance, CA, USA). The intra- and inter-assay coefficients of variation were 9 and 11%, respectively. Data are reported as ng/ml serum after comparison to NIDDK-rLH-RP1 reference samples.

Drugs

The following drugs were used: *N*-Methyl-D-Aspartic Acid (NMDA, Research Biochemicals International, RBI, USA), HEAT hydrochloride (BE 2254/2-beta-4-hydroxyphenyl-ethylaminoethyl-1-tetralone, Tocris Cookson, USA), and metoprolol (ICN Laboratories, USA). They were dissolved in saline solution and adjusted proximally to physiological pH. Estradiol benzoate and progesterone (Sigma-Aldrich, USA) were dissolved in corn oil.

Data analysis

The lordosis to mount ratio (L/M) data were analyzed by the Kruskal Wallis test followed by the Dunn's test. Hormonal values were analyzed by ANOVA 1 followed by Student Newman Kewls. In all cases, a $P < 0.05$ was considered significant. Results are given as means ± SEM.

Results

The injection of NMDA (SAL–NMDA, $N = 15$) increases L/M ratio in a very significant manner when compared with controls (SAL–SAL, $n = 27$, $P < 0.001$, Fig. 1). The injection of both doses of HEAT ($n = 22$ and $n = 29$) decreases the scores to control levels (lower dose) or even more, having the higher dose significant differences with controls ($P < 0.05$, Fig. 1).

Plasmatic LH concentrations were significantly modified by treatment [($F = 4.29$; df treatment = 3; df residual = 59, $P < 0.001$)], and increased by NMDA injection (SAL–NMDA, $n = 12$; $P < 0.05$) when compared with controls (SAL–SAL, $n = 12$, Fig. 2). The administration of HEAT in the lower dose (3 µg HEAT–NMDA, $n = 20$) was not effective to significantly decrease this values. However, a significant decrease in LH values was observed

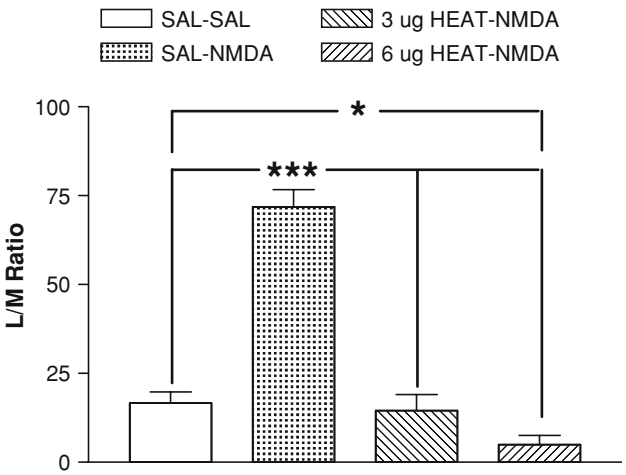

Fig. 1 Effect of HEAT on increasing effect induced by NMDA (1 µg/2 µl) on lordosis behavior in ovariectomized estradiol primed female rats. *SAL* Saline, *NMDA* *N*-methyl-D-aspartic acid, *HEAT* BE 2254/2-beta-4-hydroxyphenyl-ethylaminoethyl-1-tetralone hydrochloride. *$P < 0.05$, ***$P < 0.001$

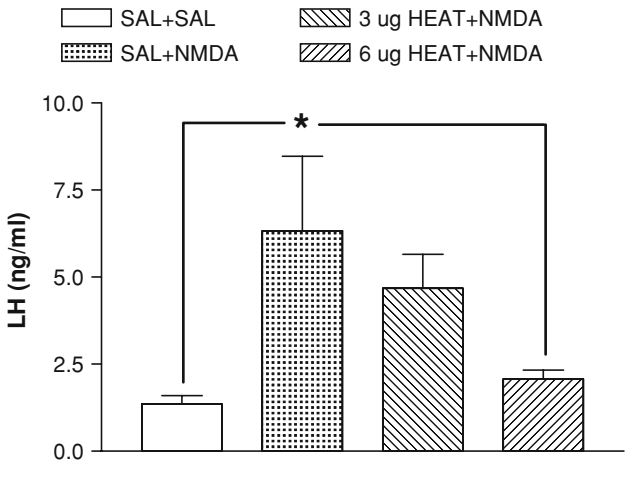

Fig. 2 Effect of HEAT on increasing effect induced by NMDA (1 μg/2 μl) on LH plasmatic values in ovariectomized estradiol primed female rats. *SAL* Saline, *NMDA N*-methyl-D-aspartic acid, *HEAT* BE 2254/2-beta-4-hydroxyphenyl-ethylaminoethyl-1-tetralone hydrochloride. $^{*}P < 0.05$

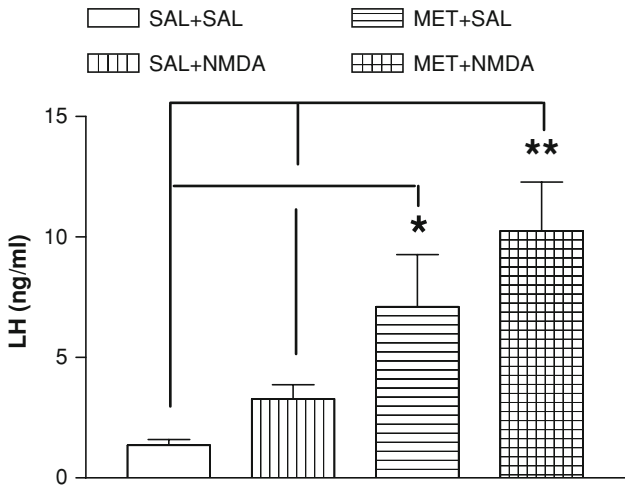

Fig. 4 Effect of Metoprolol and NMDA (0.5 μg/2 μl) on LH plasmatic values in ovariectomized estradiol primed female rats. *SAL* Saline, *NMDA N*-methyl-D-aspartic acid, *Met* metoprolol. $^{*}P < 0.05$; $^{**}P < 0.01$

when the higher dose of HEAT was administered (6 μg HEAT–NMDA, $n = 19$, $P < 0.05$) when compared with NMDA group (SAL–NMDA) leading to values that were equivalent to those of controls.

The injection of NMDA in a lower dose (SAL–NMDA 0.5 μg/2 μl, $N = 17$) and metoprolol (Met–SAL 0.5, $N = 15$) separately do not increase L/M ratio significantly when compared with controls (SAL–SAL, $n = 27$), but the combination of metoprolol and NMDA result in a potentiation of the effect on this parameter (Met–SAL, $n = 16$, $P < 0.001$, Fig. 3).

Plasmatic LH values were significantly modified by treatment [($F = 5.882$; df treatment = 3; df residual = 52, $P < 0.01$)]. They were not increased by NMDA injection at the lower dose (SAL–NMDA, $n = 14$) when compared with saline controls (SAL–SAL, $n = 12$, Fig. 4). The

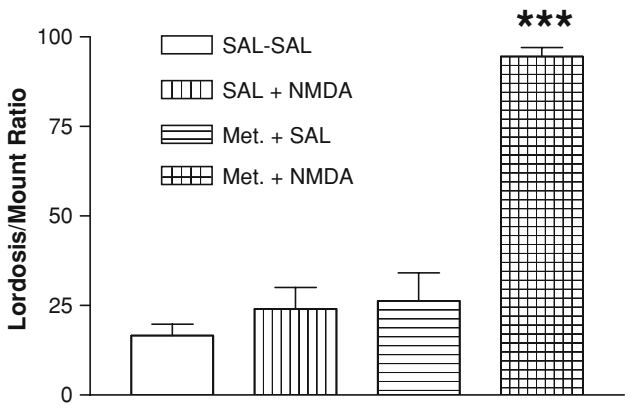

Fig. 3 Effect of Metoprolol and NMDA (0.5 μg/2 μl) on lordosis behavior in ovariectomized estradiol primed female rats. *SAL* Saline, *NMDA N*-methyl-D-aspartic acid, *Met* metoprolol. $^{***}P < 0.001$

administration of metoprolol increased by itself the LH plasmatic values (Met–SAL, $n = 15$, $P < 0.05$) when compared with saline controls, but no differences were seen when compared with the lower dose of NMDA. The combination of metoprolol and NMDA clearly enhance LH plasmatic values with differences when compared with saline controls (SAL–SAL) and SAL–NMDA (Met–NMDA, $n = 15$, $P < 0.01$). No differences were seen with metoprolol group (Met–SAL).

Discussion

Present findings extend our previous observations concerning the role of glutamate in lordosis behaviour and LH release in the same experimental schedule. These results give support to the idea that NMDA glutamatergic transmission effect on mating behavior and LH release are mediated by noradrenergic transmission.

The enhancing effect induced by the higher dose of NMDA in experiment 1 was abolished by HEAT administration ($P < 0.001$ for both doses) in lordosis/mount ratio, and the LH plasma levels were decreased only with the higher dose of HEAT ($P < 0.05$). These findings strongly suggest that the effect of NMDA in this model is mediated by α-1 noradrenergic transmission in both, behavioural and hormonal effects, and those behavioural effects are quite more sensitive to the blockade than hormonal effects. The fact that α-1 noradrenergic blockade decreased both LM ratio and LH plasmatic levels after mating is related to the stimulatory effect of this type of receptors in physiological conditions. Furthermore, the fact that α-1 noradrenergic blockade decreases significantly L/M ratio when compared

to saline controls suggests that a basal stimulation is present in these pathways. By the inverse way, in experiment 2 metoprolol enhanced both parameters considered when applied in the same conditions. Interestingly, hormonal effects were more sensitive here to the β-blockade than behavioral effects. This fact is coherent with an inhibitory role mediated by β-adrenoreceptors in physiological conditions.

The main goal of the present study was to show that both effects obtained with NMDA glutamatergic stimulation are mediated by adrenoreceptors. In this way, β-adrenoreceptors have predominance in OVX rats; the estradiol priming equiparates inhibitory and excitatory pathways, and estradiol and progesterone facilitates excitatory pathways, mediated by α-1 adrenoreceptors (Etgen et al. 1992). These effects are mediated by cyclic adenosine monophosphate (cAMP) second messenger pathway (Etgen et al. 1992). The fact that in this estradiol primed rats NMDA at the higher dose did not reach the maximal value in lordosis behaviour is an argument about the possibility that release of norepinephrine induced by this drug induces a response in which some inhibitory tone is present. The fact that the β-blockade has facilitatory action on lordosis and increases LH plasmatic values is an argument in the way that NMDA exerts their actions mediated by α-1 and β-adrenoreceptors. The fact that a lower NMDA dose (0.5 μg) in the second experiment produces higher values of lordosis behavior than in the first experiment because the combination with the β-antagonist is an additional argument in this way. The main goal of the present study is to show that both effects obtained with NMDA glutamatergic stimulation appears to be mediated by α-1 and β-adrenoreceptors.

In a previous study we observed that enhancement of lordosis induced by NMDA was not prevented by a potent LHRH antagonist, suggesting that this behavioural action of NMDA is not mediated by LHRH (Gargiulo and Donoso 1995). The role of interaction with another neurotransmitter systems was previously suggested by us (Gargiulo and Donoso 1995). In the same study, we observed that the LHRH antagonist was effective to prevent the NMDA-evoked LH release, suggesting that the endocrine effect appears to be mediated by LHRH, as it was observed in another studies (Bourguignon et al. 1989; Cicero et al. 1988; Donoso et al. 1990; López et al. 1990). Present results strongly suggest the presence of a noradrenergic mechanism mediating both effects. Furthermore, this mediation appears to be regulated by hormonal status. We have previously observed that in our previous experimental conditions in OVX female rats not primed with EB, NMDA lacked effects on lordosis and decreased plasma LH levels (Gargiulo and Donoso 1995). When these results are related with present findings, it could be hypothesized that the action of EB could be acting modifying α-1 and β-adrenoreceptors concentrations. The priming increase α-1 receptors, that has facilitatory effects on parameters here considered, and the inverse effect is observed by the mediation of β receptors (Etgen et al. 1992). The effects of NMDA could be mediated by noradrenaline release, since the α-1 blockades interferes facilitatory effects on mating behavior and LH plasmatic values, and the inverse is observed with the β blockade. Differences in hormonal status and its effect on noradrenergic receptors may explain different results reported about excitatory (Gargiulo and Donoso 1995) and inhibitory (Kow et al. 1985; McCarthy et al. 1991) effects of excitatory amino acids on lordosis responsiveness.

It could be hypothesized that axo-axonic contacts could be mediating these effects, but also stimulation of distal neurones cannot be ruled out. Excitatory amino acids are present in large concentrations in presynaptic boutons of a variety of important hypothalamic nuclei such as the arcuate nucleus, the suprachiasmatic nucleus, the supraoptic nucleus, the paraventricular nucleus, and the preoptic area (Brann and Mahesh 1994). Noradrenaline is released by excitatory amino acids from rat mediobasal hypothalamus (Navarro et al. 1994).

The possibility of the activation of distal noradrenergic somas (axo-somatic contacts) by glutamatergic neurons cannot be ruled out, and NMDA application to the locus coeruleus (LC) increases noradrenaline release in other brain areas (Kawahara et al. 2001). By the inverse way, locus coeruleus lesions decrease norepinephrine input into the medial preoptic area and medial basal hypothalamus, blocking the LH, FSH, and prolactin preovulatory surge (Anselmo-Franci et al. 1997). The activation of midbrain and brainstem noradrenergic neurons, that projects to mediobasal hypothalamus (MBH), promotes the release of LHRH from nerve terminals in the median eminence when activated by genital-somatosensory signals (Bakker and Baum 2000). In the female rabbit, norepinephrine levels increase is accompanied by a peak in LHRH values in the same samples, suggesting an interaction in this zone (Kaynard et al. 1990). In this study, they conclude that hypothalamic LHRH release is a component of reflexive ovulation in the rabbit, and the surge release of LHRH is related to an increased hypothalamic noradrenergic tone; additionally, LHRH release in the anterior hypothalamus (AH) is enhanced following coitus (Kaynard et al. 1990). In the same way, recently it has been pointed that LHRH release depends, at least in part, on locus coeruleus noradrenergic inputs to the medial preoptic area and median eminence, through an activation of LHRH neurons (Martins-Afferri et al. 2003). Additionally, LC appears to have an intrinsic cyclic activity which is amplified by ovarians steroids (Martins-Afferri et al. 2003). Recent studies using tyrosine hydroxylase (TH) mRNA expression

suggest that estradiol activation of middle and caudal A2 neurons, in conjunction with the widespread estradiol-independent activation of noradrenergic neurons in other subdivisions may play a role in the induction of LH surge release (Curran-Rauhut and Petersen 2003). Different brain zones appear to be involved in the interaction of NMDA and noradrenaline, and noradrenaline and LHRH. This study was carried giving IVT drugs, but future studies could dilucidate more precisely the zones involved.

In conclusion, present results show the noradrenergic mediation of facilitatory and inhibitory NMDA induced effects in lordosis behavior and LH plasmatic values. Our findings strongly suggest that the stimulatory effect of NMDA in this model could be mediated by α-1-adrenergic transmission and inhibitory effects by β-adrenergic transmission.

Acknowledgments We thank E. Morsucci, D.M. Videla, A. Funes, A. Morón, L. Peñafort, and J. González for their technical support, and Dr. Graciela Jahn for the LH Assay. We thank to Dr. Roberto Yunes for their comments on the present paper. We thank Dr. Juan Delius for his constant support and counseling. Pascual Angel Gargiulo, Ricardo Jorge Cabrera, and Claudia Bregonzio are established researchers of the National Council of Research (CONICET) of Argentina. Adriana Inés Landa is Research Coordinator of the Laboratory of Neurosciences and Experimental Psychology. José Vicente Lafuente Sánchez is full Professor of Neuroscience (University of the Basque Country, Spain). Angel José Martín Gargiulo and Mercedes María Lucrecia Gargiulo contributed in a very significant manner in this paper. This study was granted by CONICET (Consejo Nacional de Investigaciones Científicas y Técnicas) (PEI N° 0386/97) and a grant of Volkswagen Foundation (Germany) (Project: "Nucleus Accumbens Septi und kognitives Verhalten", Delius-Gargiulo) and is part of a cooperation with the Laboratory of General Psychology of the University of Konstanz, Germany. We thank Mrs. Sara Roitman for her invaluable cooperation. We thank Prof. Dr. Juan Delius for his constant support and counseling.

References

Ahlenius S (1993) Brain monoaminergic neurotransmission in the mediation of lordosis behavior in the female rat. Neurosci Biobehav Rev 17:43–49

Anselmo-Franci JA, Franci CR, Krulich L, Antunes-Rodrigues J, McCann SM (1997) Locus Coeruleus lesions decrease norepinephrine input into the medial preoptic area and medial basal hypothalamus and block the LH, FSH and prolactin preovulatory surge. Brain Res 767:289–296

Bakker J, Baum MJ (2000) Neuroendocrine regulation of GnRH release in induced ovulators. Front Neuroendocrinol 21(3):220–262

Bourguignon J-P, Gerard A, Mathieu J, Simons J, Franchimont P (1989) Pulsatile release of gonadotropin-releasing hormone from hypothalamic explants is restrained by blockade of N-methyl-D-aspartate receptors. Endocrinology 125:1090–1096

Brann DW, Mahesh VB (1994) Excitatory amino acids: function and significance in reproduction and neuroendocrine regulation. Front Neuroendocrinol 15:3–49

Cicero TJ, Meyer ER, Bell RD (1988) Characterization and possible opioid modulation of N-methyl-D-aspartic acid induced increases in serum luteinizing hormone levels in the developing male rat. Life Sci 42:1725–1732

Curran-Rauhut MA, Petersen SL (2003) Oestradiol-dependent and -independent modulation of tyrosine hydroxylase mRNA levels in subpopulations of A1 and A2 neurones with oestrogen receptor (ER)alpha and ER beta gene expression. J Neuroendocrinol 15:296–303

Donoso AO, López FJ, Negro-Vilar A (1990) Glutamate receptors of the non-N-methyl-D-aspartic acid type mediate the increase in luteinizing hormone-releasing hormone release by excitatory amino acids. Endocrinology 126:414–420

Donoso AO, Seltzer AM, Navarro CE, Cabrera RJ, López FJ, Negro-Vilar A (1994) Regulation of luteinizing hormone-releasing hormone and luteinizing hormone secretion by hypothalamic amino acids. Braz J Med Biol Res 27(4):921–932

Etgen AM (2003) Ovarian steroid and growth factor regulation of female reproductive function involves modification of hypothalamic alpha 1-adrenoceptor signalling. Ann N Y Acad Sci 1007:153–161

Etgen AM, Karkanias GB (1990) Estradiol regulates the number of α1 but not β or α2 noradrenergic receptors in hypothalamus of female rats. Neurochem Int 16:1–9

Etgen AM, Ungar S, Petitti N (1992) Estradiol and progesterone modulation of norepinephrine neurotransmission: Implications for the regulation of female reproductive behavior. J Neuroendocrinol 4:255–271

Gargiulo PA, Donoso AO (1995) Interaction between glutamate and luteinizing hormone releasing hormone (LHRH) in lordosis behavior and luteinizing hormone release (LH): further studies on NMDA receptor mediation. Physiol Behav 58:169–173

Gargiulo PA, Muñoz V, Donoso AO (1992) Inhibition by N-Methyl-D-aspartic acid (NMDA) receptor antagonist of lordosis behavior induced by estrogen followed by progesterone or luteinizing hormone releasing hormone (LHRH) in the rat. Physiol Behav 52:737–739

Gorzalka BB, Mendelson SD, Watson NV (1990) Serotonin receptor subtypes and sexual behavior. In: Witaker-Azmitia PM, Peroutka SJ (eds) The neuropharmacology of serotonin, vol 600. New York Academy of Sciences, New York, pp 435–446

Johnson MD, Crowley WR (1986) Role of central serotonin systems in the stimulatory effects of ovarian hormones and naloxone on luteinizing hormone release in female rats. Endocrinology 118:1180–1186

Kawahara H, Kawahara Y, Westerink BH (2001) The noradrenaline-dopamine interaction in the rat medial prefrontal cortex studied by multi-probe microdialysis. Eur J Pharmacol 418:177–186

Kaynard AH, Pau KY, Hess DL, Spies HG (1990) Gonadotropin-releasing hormone and norepinephrine release from the rabbit mediobasal and anterior hypothalamus during the mating-induced luteinizing hormone surge. Endocrinology 127:1176–1185

Kow LM, Harlan RE, Shivers BD, Pfaff DW (1985) Inhibition of the lordosis reflex in rats by intrahypothalamic infusion of neural excitatory agents: evidence that the hypothalamus contains separate inhibitory and facilitatory elements. Brain Res 341:26–34

Landa AI, Cabrera RJ, Gargiulo PA (2006) Prazosin blocks the glutmatergic effects of N-methyl-D-aspartic acid on lordosis behavior and luteinizing hormone secretion in the estrogen-primed female rat. Braz J Med Biol Res 39:365–370

Lee WW, Berghorn KA, Smith MS, Hoffman GE (1997) Alpha 1-adrenergic receptor blockade blocks LH secretion but not LHRH cFos activation. Brain Res 747:236–245

López FJ, Donoso AO, Negro-Vilar A (1990) Endogenous excitatory amino acid neurotransmission regulates the estradiol-induced LH surge in ovariectomized rats. Endocrinology 126:1771–1773

Martins-Afferri MP, Ferreira-Silva IA, Franci CR, Anselmo-Franci JA (2003) LHRH release depends on locus coeruleus noradrenergic inputs to the medial preoptic area and median eminence. Brain Res Bull 61:521–527

McCarthy MM, Curran GH, Feder HH (1991) Excitatory aminoacid modulation of lordosis in the rat. Neurosci Lett 126:94–97

Mendelson SD (1992) A review and reevaluation of the role of serotonin in the modulation of lordosis behavior in the female rat. Neurosci Biobehav Rev 16:309–350

Navarro CE, Cabrera RJ, Donoso AO (1994) Release of 3H-noradrenaline by excitatory aminoacids from rat mediobasal hypothalamus and the influence of aging. Brain Res Bull 33(6):677–682

Navarro CE, Cabrera RJ, Donoso AO (1995) Interaction between glutamate and GABA on 3H-noradrenaline release from rat hypothalamus. Brain Res Bull 37(2):119–122

Samson WK, McCann SM, Chud L, Dudley CA, Moss RL (1980) Intra- and extrahypothalamic luteinizing hormone releasing hormone (LHRH) distribution in the rat with special reference to mesencephalic sites which contain both LHRH and single neurons responsive to LHRH. Neuroendocrinology 31:66–72

Schainker BA, Cicero TJ (1980) Acute central stimulation of luteinizing hormone releasing hormone by parenterally administered N-methyl-D, L-aspartic acid in the male rat. Brain Res 184:425–437

Williams M, Totaro JA, Clineschimidt BV (1978) Interaction of 2-[beta-(4-hydroxyphenyl) ethylaminomethyl] tertralone (BE-2254: 'HEAT') with catecholamine receptors in rat brain membranes. J Pharm Pharmacol 30:390–391

Yang SP, Voogt JL (2001) Mating-activated brainstem catecholaminergic neurons in the female rat. Brain Res 894:159–166