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NMDA and group I metabotropic glutamate receptors activation modulates substance P release from the arcuate nucleus and median eminence

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Abstract

Glutamate participates in the regulation of secretion of several neuropeptides, including substance P (SP). Glutamate acts through ionotropic (iGluR) and metabotropic (mGluR) receptors. We have investigated whether glutamate receptor agonists and antagonists could affect SP release from the arcuate nucleus and the median eminence (ARC/ME). An increase in SP-like immunoreactivity (SP-LI) release from ARC/ME was induced by glutamate and *N*-methyl-D-aspartate (NMDA). This increase was prevented by D-(−)-2-amino-5-phosphono pentanoic acid (DAP5) (0.1 mM), a specific NMDA antagonist and by (RS)-1-aminoindan-1,5-dicarboxylic acid (AIDA) (0.1 mM), a selective antagonist of group I mGluR. The selective non-NMDA receptor antagonist 6,7-dinitroquinoxaline-2,3(1H-4H)-dione (DNQX) (0.1 mM) and (RS)-α-methyl-4-tetrazolylphenylglycine (MTPG) (0.1 mM), a group II and III mGluRs antagonist, did not affect the stimulatory effect of glutamate. A group I selective agonist, (*S*)-3,5-dihydroxyphenylglycine (DHPG) induced a significant increase in SP-LI release. Supporting the participation of nitric oxide (NO) in the effect of glutamate on SP-LI release, NAME (0.5 mM), a NO synthase inhibitor, reduced the glutamate-induced increase in SP-LI release from ARC/ME. Similarly, glutamate did not induce an increase in SP-LI release in the presence of meloxicam (0.1 mM) (a cyclooxygenase-2 (COX-2) specific inhibitor) indicating that prostaglandins production may also be involved in the glutamate effect. These data indicate that glutamate increases SP-LI release from the ARC/ME by acting through NMDA and group I mGluRs in the male rat. This stimulatory effect could be mediated by nitric oxide and prostaglandin production.

Keywords: Glutamate receptors; Substance P; Hypothalamus

Glutamate, the major excitatory neurotransmitter in the central nervous system (CNS), acts through both ionotropic (iGluRs) and metabotropic (mGluRs) receptors. The iGluRs have been further subdivided into *N*-methyl-D-aspartate (NMDA), kainate and alpha-amino 3-hydroxy-5-methyl-4-isoxazole propionate (AMPA) receptor subtypes [10].

mGluRs are classified into three groups. Group I mGluRs (types 1 and 5 mGluR and splice variants) increase the release of Ca^{2+} from internal stores via inositol triphosphate mobilization and activation of protein kinase C [5]. In contrast, group II mGluRs (mGluR2 and 3) and group III mGluRs (mGluR4, 6, 7 and 8) are coupled to the inhibition of adenylyl cyclase and also modulate ion channel activity [5].

Glutamate is involved in a variety of physiological and pathological processes and evidence shows that it plays an important role in neuroendocrine regulation of the hypothalamo–pituitary–gonadal axis [9]. The highest glutamate receptor density in the hypothalamus has been localized in regions related to neuroendocrine secretion and autonomic regulation [26].

The tachykinins substance P (SP), neurokinin A, and neurokinin B are neuropeptides subserving a wide range of physiological functions [8,27]. Tachykinins are widely expressed in the CNS where they have several functions such as neural modulation, often in synergy with glutamate excitatory transmission [30].

The hypothalamus is one of the main target structures innervated by tachykinin fibers projecting into the forebrain [20,24]. A large body of evidence indicates the presence of tachykinins in hypothalamic structures related to the neuroendocrine function such as the arcuate nucleus, an integrative center that receives

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dense tachykinergic innervation, specially from the preoptic area [21]. Studies using monosodium glutamate in neonatal rats showed that the arcuate nucleus is a major tachykinin containing area of the hypothalamus [18].

Considerable evidence has implicated SP in control of LH and prolactin secretion [14,15]. SP was previously shown to stimulate LH secretion and synergistically enhance GnRH-evoked LH release from cultured pituitary cells [11]. On the other hand, another studies indicate an inhibitory action of SP in the control of LH at the hypothalamic level [6,13]. Using immunohistochemistry, it has been demonstrated that certain SP/NKA neurons in the arcuate nucleus may project fibers to make synaptic contact with Gn-RH neurons in the septo-preoptic area in the rat [35]. Therefore, studying the mechanisms that control neurokinin release can provide valuable information concerning the control of hormone release.

Considering that SP participates in the control of pituitary hormone secretion and, given that iGluRs and mGluRs are involved in the regulation of the release of neurotransmitters and neuropeptides [28,29], this study investigated the effect of activation of subtypes of iGluRs and mGluRs on the release of SP from the rat arcuate nucleus and the median eminence (ARC/ME).

Male Wistar rats (200–250 g body weight) were housed under controlled temperature and light conditions. Food and water were available ad libitum. After decapitation, a hypothalamic explant including the arcuate and periventricular nuclei, the medial preoptic area and the median eminence was dissected as previously described [12]. Experiments were carried out in accordance with the National Institute of Health Guide for the Care and Use of Laboratory Animals (NIH Publications No. 80-23) revised 1996.

L-Glutamic acid (glutamate), (*S*)-3,5-dihydroxyphenylglycine (DHPG), (RS)-1-aminoindan-1,5-dicarboxylic acid (AIDA), ((2S, 1′S, 2′S)-2-(carboxycyclopropyl) glycine) (L-CCG-I), *N*-methyl-D-aspartate (NMDA), (RS)-α-methyl-4-tetrazolylphenylglycine (MTPG), D-(−)-2-amino-5-phosphonopentanoic acid (DAP5), and 6,7-dinitroquinoxaline-2,3(1H–4H)-dione (DNQX) were purchased from Tocris Cookson Inc. (Ballwin, MO, USA). *N*ω-Nitro-L-arginine methyl ester hydrochloride (NAME) and 4-Hydroxy-2methyl-*N*-(5-methyl-2thiazolyl)-2H-1,2-benzothiazine-3-carboxamide1,1-dioxide (Meloxicam) were purchased from Sigma Aldrich Co (St. Louis, MO, USA). ^{125}I-[Tyr^{8}]SP was obtained from New England Nuclear^{TM} (Boston, MA, USA).

	Antagonist
NMDA receptor	DAP5
AMPA/KA receptor	DNQX
Group I mGluRs	AIDA
Group II/III mGluRs	MTPG

Two ARC/ME fragments were incubated in a Dubnoff shaker at 37 °C, in 95% O_2 −5% CO_2 with 0.5 ml of Krebs–Ringer bicarbonate (KRB) buffer (119 mM NaCl, 5 mM KCl, 2.5 mM $CaCl_2$, 1.2 mM $NaHPO_4$, 1.2 mM $MgSO_4$, 25 mM $NaHCO_3$) pH 7.4, with 10 mM glucose, 25 mM HEPES, 0.1% bovine serum albumin (BSA) and 0.1 mM bacitracin.

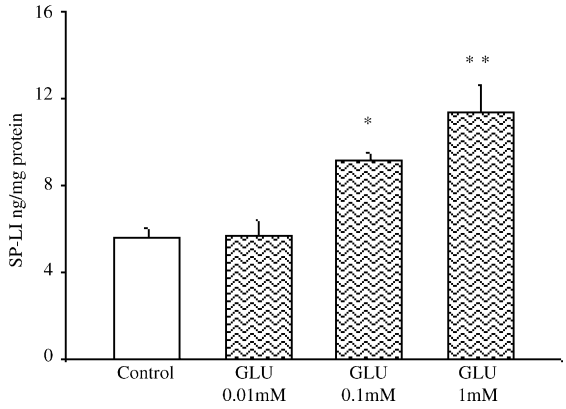

Fig. 1. Glutamate increases SP-LI release from ARC/ME of male rats. Data were expressed as the mean ± S.E.M. of five determinations per group. $^{*}p < 0.05$ and $^{**}p < 0.01$ vs. control group.

Tissues were preincubated for 15 min. Then the medium was replaced with fresh KRB and the tissues were incubated for 30 min in the presence of agonists and/or antagonists. At the end of the incubation, the medium was frozen and lyophilized until assayed for SP-like immunoreactivity (SP-LI). The tissues were homogenized in 2 N acetic acid and protein concentration was determined by the Bradford method.

The concentration of SP-LI was quantified by radioimmunoassay (RIA) previously described in detail [7]. The SP antibody was purchased from Bachem AG. The tracer was ^{125}I-[Tyr^{8}]SP (New England Nuclear) and the sensitivity of the assay was 15 pg SP-LI/tube. The inter- and intra- assay coefficients of variation were less than 6 and 11%, respectively.

Data were expressed as the mean ± S.E.M. and were analyzed by one- or two-way analysis of variance (ANOVA) followed by Dunnett's test for comparisons against the control group or by Bonferroni Test for multiple comparisons. Differences were considered statistically significant when $p < 0.05$. All experiments were performed at least twice. Figures represent results of individual experiments.

Glutamate increased the release of SP-LI from ARC/ME of male rats at 0.1 and 1 mM (Fig. 1). To investigate which type of glutamate receptor was involved in the effect of glutamate on SP-LI release, we determined the effect of different agonists and antagonists of glutamate receptors. A specific NMDA antagonist, DAP5 0.1 mM, and a specific group I mGluR antagonist, AIDA 0.1 mM, prevented the stimulatory effect of glutamate 1 mM on SP-LI release (Fig. 2A and B). On the contrary, an AMPA/KA antagonist (DNQX 0.1 mM) and a group II/III mGluR antagonist (MTPG 0.1 mM) failed to modify SP-LI release induced by glutamate (Fig. 2A and B). NMDA at 0.1 and 1 mM increased the release of SP-LI from ARC/ME (Fig. 3A). DHPG, a group I agonist also increased SP-LI release at all concentrations tested (Fig. 3B).

Since glutamate is known to induce the expression and activity of inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2), we tested the effect of an iNOS inhibitor (NAME) and a COX-2 inhibitor (Meloxicam). The

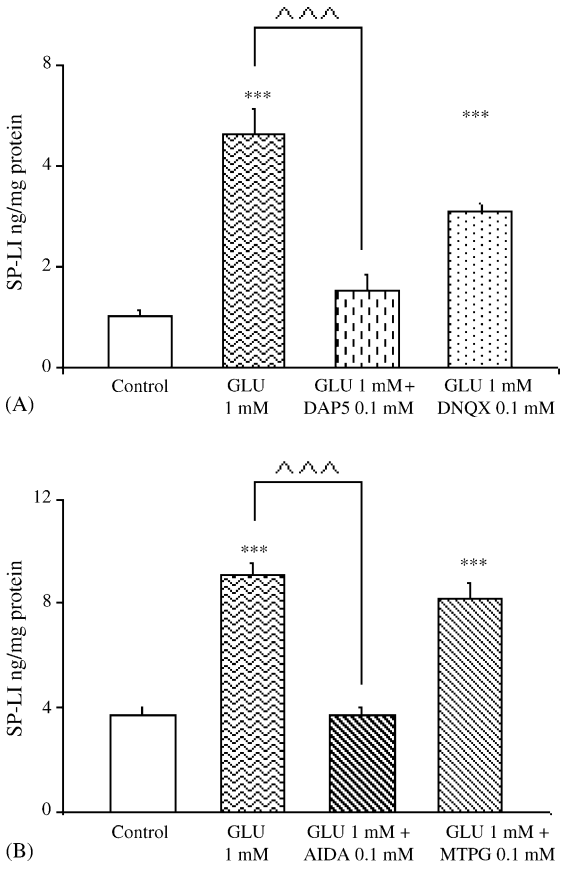

Fig. 2. Effect of: (A) glutamate alone or in the presence of D-AP5 (NMDA antagonist) and DNQX (AMPA/KA antagonist) and (B) glutamate alone or in the presence of AIDA (group I mGluR antagonist)or or MTPG (group II/III mGluR antagonist) on the release of SP-LI from ARC/ME. Data were expressed as the mean ± S.E.M. of five determinations per group. $^{***}p < 0.001$ vs. control group, $^{\wedge\wedge\wedge}p < 0.001$ vs. glutamate 1 mM.

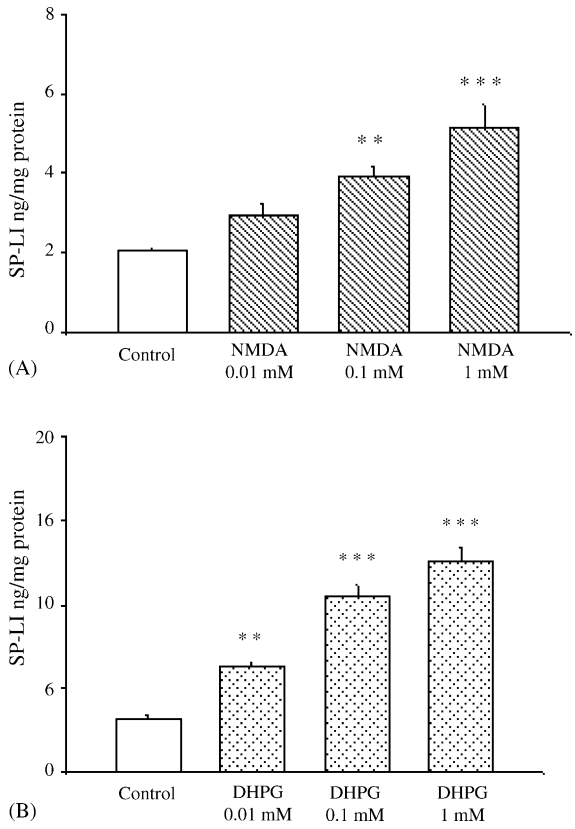

Fig. 3. NMDA (A) and DHPG (group I mGluR agonist) (B) increased SP-LI release from ARC/ME. Data were expressed as the mean ± S.E.M. of five determinations per group. $^{**}p < 0.01$ and $^{***}p < 0.001$ vs. control group.

iNOS inhibitor NAME did not modify the release of SP-LI per se, but did block the stimulatory effect of glutamate on SP-LI release from ARC/ME (Fig. 4A). In a similar way, the presence of the COX-2 inhibitor Meloxicam, reduced glutamate-induced increase in SP-LI release from ARC/ME (Fig. 4B).

The present study provides evidence supporting the hypothesis that glutamate-induced release of SP-LI in the ARC/ME is mediated via activation of NMDA and group I mGluR receptors. However, the AMPA/KA receptors and group II and III mGluR receptors do not appear to contribute to SP-LI release. These data are consistent with previous reports on the effect of NMDA on spinal SP release in vivo and in vitro [1,22]. Moreover in the spinal cord, the high affinity SP receptor (NK-1) internalization studies suggest that activation of presynaptic NMDA receptors induces the release of SP from primary afferents [19,25].

Previous studies also suggest that glutamatergic transmission mediated by NMDA receptor serves as a tonic signal to stimulate SP biosynthesis in the striatum [32] and that SP release in this area is selectively mediated by the NMDA receptor [16]. Moreover, glutamate and SP colocalize in the suprachiasmatic nucleus [31]. Previous findings provide anatomical evidence to show that NK-1 is linked to glutamate neurons in the anterior medial hypothalamus [38].

mGluRs modulate neurotransmission in synaptic terminals throughout the brain [5] and act presynaptically to reduce transmission at glutamatergic synapses [29]. Our present results indicate that activation of group I mGluRs induces an increase in SP release. Accordingly, selective activation of group I metabotropic receptors upregulates SP mRNA expression in rat dorsal striatum [23].

Glutamate is believed to elicit many of these effects by activating the release of the gaseous neurotransmitter, nitric oxide (NO) [4]. NO is also involved in the release of neurotransmitters such as SP [39].

We studied the role of NO in the effect of glutamate on SP release in rat ARC/ME fragments, a hypothalamic structure known to contain a rich plexus of NOS-containing neurons and fibers together with densely arranged glutamate-receptor-like immunoreactive fibers. We found that the stimulatory effect of glutamate was not observed in the presence of NAME, an inhibitor of NOS. These observations suggest that NO makes a major contribution to the response of the ARC/ME to glutamate.

NO potently stimulates GnRH by activating a heme containing enzyme, guanylate cyclase, which in turn leads to increased production of cGMP and GnRH release. There is evidence that some of the effects of glutamate on GnRH release may involve activation of the nitric oxide and possibly catecholamines [9].

Glutamate plays a key role in important neuroendocrine events such as puberty, pulsatility, the midcycle surge of gonadotropins and reproductive behavior [9]. However, much

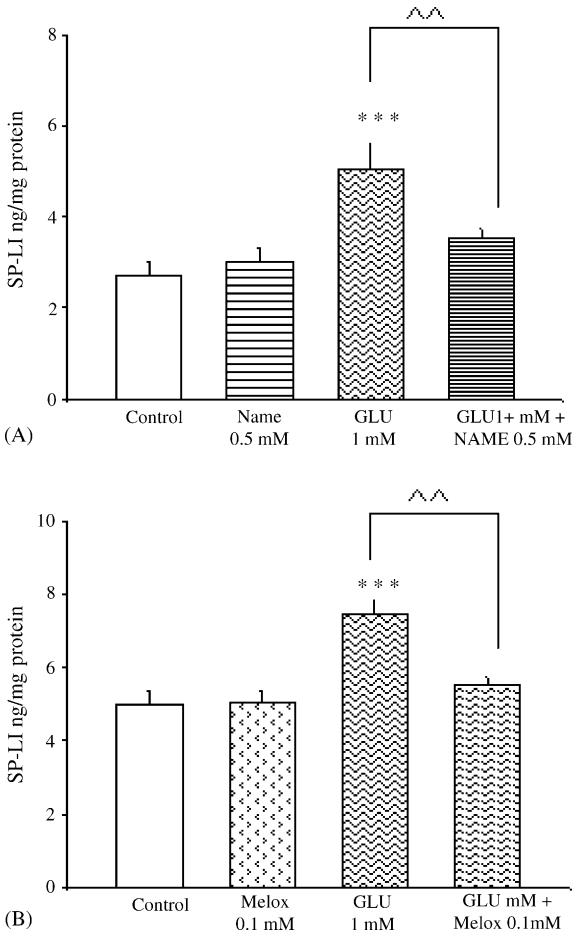

Fig. 4. A. NAME (0.5 mM), a NOS inhibitor, blocked the increase of the glutamate-induced SP-LI release from ARC/ME. B Meloxicam (0.1 mM), a COX-2 inhibitor, decreased the glutamate-induced SP-LI release from ARC/ME. Data were expressed as the mean ± S.E.M. of five determinations per group. $^{***}p < 0.001$ vs. control group, $^{\hat{}\hat{}}p < 0.01$ vs. glutamate 1 mM.

work lies ahead to further characterize important mediators of glutamate signaling.

The regulation of prolactin and LH release from the anterior pituitary is complex and involves several factors including SP [14,15]. It has been demonstrated that SP enhances prolactin release by a direct action on the anterior pituitary. Dopamine, the major prolactin inhibitory factor, decreases hypothalamic SP release [17]. On the other hand, our results indicate that glutamate increases hypothalamic SP release. This action could lead to an increase in prolactin, reinforcing the stimulatory action of glutamate on this hormone. On the other hand, SP and other tachykinins exert an inhibitory action on LH secretion at the level of the hypothalamus but induce excitatory effects at the anterior pituitary level [8]. The effect of these peptides may be exerted at different levels, on cell bodies of GnRH neurons in the preoptic area, on nerve terminals in the median eminence or indirectly through modifications in other neurotransmitter systems. Also, the activation of different receptor subtypes may induce different responses of tachykinins on LH secretion [8].

Since glutamate has been shown to play an important role in the regulation of pulsatile gonadotropin release and preovulatory and steroid-induced gonadotropin surges [9], the increase of SP release induced by glutamate may contribute to glutamate effects on LH secretion.

Over the last few years, experimental evidence has accumulated to demonstrate that the stimulation of mGluRs induces the calcium-dependent production of arachidonic acid metabolites including PGE_2 [3]. Recently, it was demonstrated that prostaglandin release from astrocytes depends mainly on mGluR-mediated [Ca^{2+}] oscillations [40]. Neuronal COX-2 expression is upregulated following brain insults, via glutamatergic and inflammatory mechanisms. Glutamate, NMDA and kainate increase COX-2 mRNA in cerebellar granule neurons [33]. The products of COX-2 are bioactive prostanoids and reactive oxygen species that contribute to toxicity associated with inflammation.

During inflammation, a number of molecules, including prostaglandins, bradykinin, substance P, glutamate and others, are released into injury site [37]. The cytotoxic effects of chronic neuroinflammation may involve prostanoid synthesis and may operate through NMDA receptors [36]. NMDA receptors contribute to evoked SP release in the setting of inflammation in the dorsal horn [2]. A recent study, suggests that SP-governed cascade leading to PGE_2 elevation is completely linked to the upstream event of NMDA receptor activation [34].

We found that the stimulatory effect of glutamate on SP release was blocked in the presence of meloxicam, an inhibitor of COX-2, suggesting that prostaglandins are involved in the effect of glutamate in the ARC/ME. It is possible that glutamate and SP are also involved in inflammatory processes in the hypothalamus and that SP release might enhance the inflammatory response induced by glutamate, since SP released from neurons following NMDA receptor activation plays a critical role in promoting systemic oxidative stress.

In summary, our data show that glutamate induces an increase in SP release from ARC/ME by acting through NMDA and group I mGluR by a mechanism involving NO and prostaglandin production. Therefore, the release of SP in the ARC/ME appears to be controlled by NMDA and group I mGluR.

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