# The role of ATP sensitive P2 receptors in the regulation of the hippocampal neurotransmitter (noradrenaline, GABA, glutamate) release: bring into focus the $P2X_7$ receptor

**Ph.D. thesis**

**Lilla Papp**

**Semmelweis University**

**John Szentágothai School of Ph.D. Studies**

**Supervisior:** Dr. Beáta Sperlágh Scientific advisor Ph.D. D.Sc.

**Scientific Referees:** Dr. László Köles Assistant professor Ph.D.

Dr. Zsuzsanna Helyes Associate professor Ph.D.

**Committee Members at the Comprehensive Exam:**

Chairmen: Dr. Klára Gyires Full professor, head of Department Ph.D. D.Sc.

Dr. András József Szentmiklósi Associate professor Ph.D.

Dr. Zsófia Nemoda Assistant professor Ph.D.

**Budapest, 2009.**

## I. Introduction

ATP is an important extracellular messenger in the central nervous system playing roles as a neurotransmitter and presynaptic modulator. The action of ATP are conveyed by ionotropic P2X ($P2X_{1-7}$) and metabotropic P2Y ($P2Y_{1,2,4,6,11,12,13,14}$) receptors in the extracellular space. Previous studies showed that activation of P2X receptors leads to an increased release of neurotransmitters in several central and peripheral synapses by the influx of $Ca^{2+}$ through the receptor ion channel complex, however, the exact subunit composition of receptors involved in this response had not been explored yet at the beginning of our studies. Among P2X receptors the slowly desensitizing $P2X_7$ receptor is unique having an extended carboxy terminal domain, which contains a LPS (lipolysaccharide) binding site. $P2X_7$ receptors are activated by higher ATP concentration (mM), and their sustained or repeated stimulation leads to the formation of a reversible plasmamembrane pore, permeable up to 800 Da. The $P2X_7R$ was first described as P2Z receptor, as a cell-death receptor, mediating the cytotoxic effects of ATP, inducing apoptosis or necrosis. The $P2X_7Rs$ are expressed by many cell types, like mast cells, endothelial and epithelial cells, immune cells (monocytes, macrophages, dendritic cells, T-B lymphocytes), glial cells (microglia, oligodendroglia, Schwann cells, astrocytes), neurones (sympathic-and enteric neurones, dorsal root-and retinal ganglion neurones, cerebellar granule cells, hippocampal-cortical pyramidal cells and interneurones). $P2X_7Rs$ have also been identified at presynaptic nerve terminals, suggesting a role in synaptic transmission in physiological and pathological

conditions. The $P2X_7Rs$ may function as a molecular sensor of the increased neural activity, and thereby they might have a role in the plasticity phenomena underlying learning and memory (LTP, LTD). In addition, $P2X_7Rs$ may have an aggravating role in the neurodegenerative and inflammatory diseases of the nervous system (e.g. ischemia, Alzheimer's disease, multiple sclerosis), because they participate in the regulation of the release of numerous proinflammatory cytokines (such as IL-1β, TNF-α, IFN-γ) and chemokines (e.g. MIP-macrophage inhibitor protein) and activate their downstream signaling pathways at enzymatic (e.g. MAPKs - mitogen activated protein kinases, PLA2/PLD-phospholipaseA2/D, caspases) and transcription factor ( NF-kB-nuclear factor kB, AP-1-activator protein-1, CREB-cyclic AMP response element (CRE)-binding protein) level. Thus $P2X_7R$ antagonists are developed as new antiinflammatory therapeutic agents by several pharmaceutical companies (e.g. Astrazeneca, Pfizer).

## II. Objectives

**II/1. To explore the role of P2 receptors in the regulation of NA release in the rat hippocampus:** we addressed the question whether the activation of the ionotropic P2 receptors may release noradrenaline (NA) from the terminals of the catecholaminergic neurones of the brain and if so, what purinoceptor subtypes mediate this effect.

**II/2. To explore the role of $P2X_7$ receptor in the regulation of GABA and glutamate release in the mouse hippocampus:** In order

to find out whether ATP, acting at $P2X_7Rs$ is able to modify the release of GABA and glutamate in the hippocampal slices of $P2X_7R$ wild type and KO mice.

**II/3. To explore the role of the $P2X_7$ receptor and the p38 MAPK in the regulation of glutamate release in the mouse hippocampus:** we examined, whether $P2X_7R$ activation promotes p38 MAPK phosphorylation in the hippocampus and if so, whether this signaling event mediates the facilitatory effect of ATP on the release of glutamate in mouse hippocampal slices.

## III. Methods

All studies were conducted in accordance with the principles and procedures outlined in the NIH Guide for the Care and Use of Laboratory Animals, and were approved by the local Animal Care Committee of the Institute of Experimental Medicine.

The original breeding pairs of $P2X_7R$ -/- (KO) mice (C57BL/6J based) were supplied by Christopher Gabel from Pfizer Inc. (Groton CT, USA). The animals contained a DNA construct, where a part of gene encoding the $P2X_7R$ was replaced with a gene encoding neomycin resistance, resulting in the genetic deletion of the gene coding the $P2X_7R$, and the lack of functional $P2X_7R$ protein in homozygous $P2X_7R$ -/- (KO) mice. All experiments using mice were conducted on 3–5 months old, homozygous ($P2X_7R$-/-) male mice weighing 20–25 g; their wild-type (WT) littermates ($P2X_7R$ +/+) were used as controls. Genomic DNA was isolated from the tails of WT and $P2X_7R$ -/-

animals and their genotypes were confirmed by PCR analysis using gene-specific primers as described by Solle and coworkers.

**III/1. [$^3$H]NA, [$^3$H]Glutamate ([$^3$H]GLU) and [$^3$H]GABA release experiments from rat/mouse hippocampal slices:** Briefly, mice described above and 31-36 days old, male Wistar rats weighing 120-140 g, (Charles Rives Hungary) in the NA experiments were anesthetized under light $CO_2$ inhalation and then decapitated. The hippocampi were dissected in ice-cold Krebs' solution saturated with 95%$O_2$ and 5%$CO_2$ and 400 μm thick slices were prepared by McIIwain tissue chopper and incubated in 1ml of modified Krebs' solution (mM: NaCl 113, KCl 4.7, $CaCl_2$ 2.5, $KH_2PO_4$ 1.2, $MgSO_4$ 1.2, $NaHCO_3$ 25.0, glucose 11.5, pH 7.4) containing 5 μCi/ml [$^3$H]glutamic acid (1.74 TBq/mmol) or 5 μCi/ml [$^3$H]GABA (3.44 TBq/mmol) and β-alanine (1mM); the latter to prevent tritium uptake into glial cells, or in the NA experiments: ascorbic acid (30 μM), $Na_2EDTA$ (100 μM), and 5 μl [$^3$H]NA, (370 kBq/ml, Amersham) for 45 min. The medium was bubbled continuously with 95% $O_2$ and 5% $CO_2$ and maintained at 32°C in the GLU experiments and at 37°C in the GABA and NA experiments. After loading, the tissue samples were rinsed three times with Krebs solution in a test-tube carefully, then transferred into one of four polypropylene tissue chambers and superfused continuously with 95% $O_2$ and 5% $CO_2$ saturated modified Krebs solution (in the GABA experiments, also containing 0.1 mM aminooxyacetic acid). Subsequently, 3 min perfusate samples were collected and assayed for [$^3$H]NA, [$^3$H]GLU and [$^3$H]GABA. Two

consecutive electrical field stimulation periods ($EFS_1$, $EFS_2$) were applied by a Grass S88 stimulator (Quincy, MA, USA; 10 Hz, 720 shocks, 1 ms, [$^3$H]GLU: 40V, [$^3$H]GABA: 35 V). In other experiments preparations were subjected to 6 min perfusion of agonist (e.g. ATP) in the absence or presence of drugs (eg. pyridoxalphosphate-6-azophenyl-20,40-disulphonic acid tetrasodium (PPADS), Brilliant blue G (BBG), SB203580, PD098095, all from Sigma), which were preperfused 30 min before the second agonist application. The radioactivity released from the preparations was measured with a Packard 1900 Tricarb liquid scintillation spectrometer. The release of [$^3$H]NA, [$^3$H]GLU and [$^3$H]GABA was expressed as a percentage of the amount of radioactivity in the tissue at the sample collection time (fractional release). The tissue tritium uptake was determined as the sum release + tissue content after the experiment and expressed in Bq/g. Basal outflow was calculated as the fractional release measured in a 3-min sample in the absence of drugs. Electrical field stimulation-induced ($EFS_1$, $EFS_2$) and agonist induced ($S_1$, $S_2$) [$^3$H]NA, [$^3$H]GLU and [$^3$H]GABA efflux were expressed by calculating the net release in response to the respective stimulus by subtracting the release before the stimulation from the values measured after stimulation. The effect of drugs on the agonist-evoked release of [$^3$H]NA, [$^3$H]GLU and [$^3$H]GABA was expressed as $S_2/S_1$ ratios measured in the absence and presence of the drugs.

**Statistics:** All data were expressed as means ± s.e.m. of *n* observations. The statistical analyses were made by one way analysis

of variance (ANOVA) followed by the Dunnett's post hoc test (multiple comparisons), or Student's t-test (pairwise comparisons). P <0.05 was considered statistically significant.

**III/2. Western blot analysis from mouse hippocampal slices:** Hippocampal slices (400 μm) were prepared from C57BL/6J based WT $P2X_7R$ +/+ and $P2X_7R$ -/- (KO) mice and dissected in ice-cold $Ca^{2+}$-free artificial cerebrospinal fluid (ACSF; in mM: NaCl 125; KCl 2.4; $MgCl_2$ 0.83; $CaCl_2$ 1.1; $KH_2PO_4$ 0.5; $Na_2SO_4$ 0.5; $NaHCO_3$ 27; glucose 10; Hepes 110, pH 7.4; $Ca^{2+}$-free ACSF was of the same composition except for 1.93 mM $MgCl_2$). The slices were placed for 10 min in polypropylene tubes containing $Ca^{2+}$-free ACSF at 35 °C, equilibrated at pH 7.4 in $O_2/CO_2$ (95:5, v/v), and incubated at 35 °C in 900 μL ACSF containing 1.1 mM $Ca^{2+}$ and 1 μM tetrodotoxin (TTX) for 50 min before pharmacological treatment. ATP (1 mM), and BzATP (100 μM) were added for 5 min, whereas P2 purinoceptor antagonists (PPADS, 30 μM and BBG, 1 μM) and the p38 MAPK inhibitor SB203580 (1 μM) was allowed to react for 30 min after the incubation. The ACSF solution was then aspirated and the slices were lysed by sonication in homogenization buffer containing 1% sodium dodecyl sulphate (SDS; v/v), 1 mM sodium orthovanadate (phosphatase inhibitor) and 1 μL of protease inhibitor cocktail (Sigma), with sterile water added to a total volume of 100 μL. After centrifugation (4 °C, 10000 rpm, 15 min), the protein concentration of the upper solution of each sample was measured using Folin reagent. The samples were prepared by boiling in sample buffer, and equal

amounts of protein (70 μg) were separated by tris-glycine-SDS–polyacrylamide gel electrophoresis (10%) and transferred onto a nitrocellulose membrane using a MiniProtean-3 (Bio-Rad) apparatus. The membranes were then blocked with 5% dry milk in tris-buffered saline Tween 20 (TBST) buffer for 1 h at room temperature, incubated with p38C-20 primary antibody (1:500) for 1 h and washed in TBST buffer for 10 min three times. Before applying the P-p38 antibody (1:1000) for 2 h at room temperature, the membranes were blocked with 1% BSA in TBST buffer overnight at 4 °C, then washed with TBST buffer for 10 min three times. The membranes were incubated with secondary antibody (donkey anti-rabbit IgG-HRP, 1:3000 relative to the p38 C-20 primary antibody and 1:5000 relative to the P-p38 primary antibody) for 1 h at room temperature. The specific bands were detected and visualized by chemiluminescence. The quantification of the immunoreactive bands was performed using the SynGene program by densitometer analysis.

**III/3. RT-PCR study:** Male Wistar rats (120–140 g) were decapitated under light $CO_2$ anesthesia, and the brain was quickly put into ice-cold Krebs' solution oxygenated with 95% $O_2$ and 5% $CO_2$. The brainstem was rapidly dissected and collected in liquid nitrogen. Total RNA from brainstem samples was isolated with TriPure Isolation Reagent according to the protocol provided by the supplier. RNA samples dissolved in diethyl pyrocarbonate-treated water were checked on formaldehyde containing agarose gel and were quantified by absorbance at 260 nm. RNA (1 μg, 2 μl) was reverse transcribed with

RevertAid First Strand cDNA Synthesis Kit using random hexamer primers. Aliquots of the first strand cDNA were amplified by PCR using 0.4 μM (1.1 μl) forward and reverse primers and 2 U (0.3 μl) of TaqDNA polymerase. Primers for amplification of different forms of p2x and p2y receptor cDNAs and β-actin primers for control amplification were identical to that used in our previous study. The GenBank accession numbers were as follows: p2x1, NM_012997; p2x2, U14414; p2x3, NM_031075; p2x4, X91200; p2x5, X92069; p2x6, X97376; p2x7, NM_019256; p2y1, U22830; p2y2, NM_017255; p2y4, NM_031680; p2y6, D63665; and β-actin, X03765. The conditions for amplification were as follows: initial denaturation at 95°C, 5min, hot start at 80°C, then 94°C, 1min, 59°C, 1min, and 72°C, 1min for 40 cycles, with a final extension at 72°C, 5min. PCR products were analyzed by agarose gel electrophoresis.

## IV. Results

### IV/1. The involvement of facilitatory P2X receptors in the regulation of the tritiated noradrenaline release in the rat hippocampus

**A.** In our experiments, ATP perfusion elicited concentration-dependent efflux of [$^3$H]NA from rat hippocampal slices. To identify potential P2X and P2Y receptor subtypes, responsible for the ATP-evoked tritiated noradrenaline release, **RT-PCR analysis** was performed in the rat brainstem, containing catecholaminergic nuclei projecting to the hippocampus. In the analysis, positive signal was

detected in the case of mRNA encoding $P2X_{1,2,3,4,6,7}$ and $P2Y_1$ receptors, while signal for mRNA encoding $P2X_5$ and $P2Y_{2,4,6}$ receptors were absent.

It is important to note, however, that the presence of mRNA encoding P2X and P2Y receptor subtypes in the whole brainstem, do not imply their expression in the noradrenergic cell bodies of locus coeruleus and the mRNA levels do not necessarily reflect the expected level of protein expression, therefore we examined the individual P2 receptor subtypes **pharmacologically** as well.

**B.** Using different P2-receptor agonists we found that ATP, α,β-MeATP and ADP all elicited NA efflux in the hippocampus with the following order of potency: α,β-MeATP > ATP ≥ ADP. Among P2X receptors with known pharmacological profile, $P2X_1$, $P2X_3$, $P2X_{2/3}$ $P2X_{1/5}$, $P2X_{1/2}$, and $P2X_{4/6}$ receptors are activated by α,β-Me-ATP, however, the involvement of $P2X_{1/5}$ receptors was ruled out by PCR analysis. As for the $P2X_{4/6}$ receptor, because α,β-MeATP is only a partial agonist at this subtype, its involvement in the effect seems also unlikely.

**C.** As for P2 antagonists, PPADS (30μM), NF023 (10μM) and NF449 (100nM), significantly inhibited ATP (10mM) evoked [$^3$H]NA outflow, whereas BBG (100nM) and MRS2179 (10μM) were ineffective.

**D.** Pretreatment with Gi protein inhibitor pertussis toxin (2.5 mg/ml) did not change ATP evoked [$^3$H]NA release, therefore the role of P2Y receptors, at least those coupled to Gi proteins, might be excluded.

**E.** Since it is known that lowering the pH differentially affects the response mediated by individual P2X receptor subunits, the effect of a change in the extracellular pH was tested. Lowering the extracellular pH from 7.4 to 6.5 significantly inhibited ATP evoked [$^3$H]NA efflux, which is in agreement with the involvement of $P2X_1$ and $P2X_3$ receptors but argues against the involvement of the $P2X_{1/2}$ and $P2X_{2/3}$ receptors, which respond to the acidic environment with potentiation.

**F.** Finally, $A_1$ and $A_{2A}$ adenosine receptors as well as the heteromeric $P2Y_1/A_1$ receptors were taken into account. Nevertheless, DPCPX and DMPX, antagonists of these receptors, were inactive at the inhibition of the response elicited by ATP.

**G.** We also identified the underlying mechanism responsible for the effect of ATP to release [$^3$H]NA in our experiments. Being unaffected by TTX, action potential propagation seems to play a minor role in this effect. On the other hand, in the presence of the NMDA and non-NMDA receptor antagonists AP-5 (50μM) and CNQX (10μM), the ATP evoked [$^3$H]NA release was decreased, indicating that the effect of ATP is partly mediated by glutamate receptor activation. Omission of $Na^+$, but not $Ca^{2+}$ from the perfusion medium abolished ATP evoked [$^3$H]NA outflow, which implies that the mechanism responsible for the action of ATP is a direct influx of sodium through the receptor ion channel complex. The $Ca^{2+}$ independent nature of ATP influx also indicate that this release is originated from the cytoplasm and have nonvesicular origin. Moreover, the [$^3$H]NA outflow evoked by ATP was completely abolished by the noradrenaline transporter inhibitor desipramine, which indicates that

[$^3$H]NA released from the cytoplasm by the $Na^+$-dependent reversal of the noradrenaline transporter.

### IV/2. The role of $P2X_7$ receptors in the modulation of glutamate and GABA release in mouse hippocampus

**A.** The genetic deletion of the $P2X_7$ receptor in the $P2X_7R$ -/- KO mice was confirmed by PCR analysis. A 425 bp fragment size product was detected in wild type (WT) mice, whereas a 200bp size band was detected in $P2X_7R$ -/- KO mice, which corresponds to the neomycin resistance gene cassette sequences and which was absent in wild type mice.

**B.** Electrical field stimulation elicited a reproducible increase in the tritiated GLU and GABA outflow in the hippocampal slices of WT mice, which was lower in KO mice, whilst no significant change was found in the uptake of radioactivity and in basal outflow.

**C**. Perfusion of ATP (10mM) elicited well detectable and reproducible GLU and GABA release in WT mice, and the amount of the tritium outflow was similar to those detected in response to electrical field stimulation, however, this action was almost completely abolished in the hippocampal slice of KO mice.

**D.** The P2X receptor antagonist PPADS (30μM), which acts at several subtypes of P2 receptors, as well as the $P2X_7R$ selective antagonist Brilliant Blue G (BBG, 1μM) significantly decreased the ATP (10mM) evoked tritiated GLU and GABA release in the hippocampal slices of WT mice, and the effect of PPADS was more pronounced.

**IV/3. The subcellular signaling mechanism of the $P2X_7$ receptor activation in the hippocampal slices of mouse**

**A.** We explored that ATP (10mM), the endogenous ligand and BzATP (100μM), the agonist of the $P2X_7R$ increased the expression of active form of the p38 MAPK in the hippocampal slice of wild type mice, BzATP being the more potent among them; and this effect was absent in the $P2X_7R$ -/- KO mice.

**B.** These changes were sensitive to the specific inhibitor of the p38 MAPK, SB203580 (1μM).

**C.** One functional consequence of the $P2X_7R$ activation, the enhanced glutamate release is mediated by p38 MAPK, because SB203580 (1μM) inhibited significantly the ATP (10mM) evoked tritiated glutamate release, whereas PD098095 (the ERK1/2 inhibitor) was ineffective in the hippocampal slice of the WT mice.

**V. Most important conclusions**

**V/1.** We measured a remarkable increase in the [$^3$H]NA outflow by the stimulation of rat hippocampal slices with 10 mM ATP. On the basis of our experiments this kind of NA release is partly the consequence of the activation of NMDA and non-NMDA receptors, however action potential seems not to play a role in this effect. Its hypothetical mechanism is the primary $Na^+$ influx across the receptor ion-channel complex, and the subsequent reversal of the $Na^+$ dependent NA transporters. At the pharmacological identification of

P2 receptors responsible for these effects we have taken into account **1.** the agonist profile **2.** the sensitivity of the effect to antagonists **3.** the changes in receptor function by acidification of extracellular pH. We conclude that the facilitatory P2X receptors, and among them probably the homomer $P2X_1$ or the homomer $P2X_3$ receptors regulate NA release in the rat hippocampus.

**V/2.** The lack of the effect of ATP on the release of GABA and GLU in the $P2X_7R$ -/- KO mice, and the observation that PPADS and BBG treatment inhibited both the tritiated GABA and GLU release, support the assumption that the $P2X_7R$ mediated GABA outflow is the consequence of the $P2X_7R$ mediated GLU release and subsequent activation of the non-NMDA glutamate receptors. Glutamate outflow, measured in our experiments, however, might be not only synaptic, but also non-synaptic and may have non-neuronal origin as well. By contrast, we suppose that the tritiated GABA outflow is neuronal, because the tritium uptake of the glial cells was blocked by beta-alanin under incubation, moreover it has been previously proven that the tritiated GABA release evoked by ATP is sensitive to the inhibition of glutamate receptors and TTX, the latter prevents axonal activity. The significant decrease in the tritiated GABA and GLU release evoked by electrical field stimulation in the hippocampal slices of the $P2X_7R$ -/- KO mice can be explained in a way that the endogenous ATP release, evoked by neuronal activity increases the release of glutamate and GABA by $P2X_7R$ activation, and the latter is derived from the interneuron targets of the facilitatory nerve terminals.

Thus, $P2X_7Rs$ may participate in the regulation of the extraneuronal glutamate and GABA levels under synaptic activity.

**V/3.** We report here for the first time the increased p38 MAPK enzyme expression following $P2X_7R$ activation in the mouse hippocampus. The p38 MAPK phosphorylation regulated by $P2X_7R$ activity may originate from neurons, astrocytes and microglia as well. The activation of the $P2X_7R$ could either lead to a direct interaction with the p38 MAPK enzyme, but we cannot exclude the possibility that the increased p38 activity is the secondary consequence of further subcellular events caused by $P2X_7R$ activation. This interaction may play an important role in the increased glutamate release and other neuronal effects following the $P2X_7R$ activation under such physiological and pathological conditions (e.g. synaptic plasticity, neurodegeneration, neuroinflammation), where both $P2X_7Rs$ and p38 MAPKs are known to be activated.

## VI. My publications

**Papp L**, Balázsa T, Kőfalvi A, Erdélyi F, Szabó G, Vizi ES, Sperlágh B. (2004) P2X receptor activation elicits transporter-mediated noradrenaline release from rat hippocampal slices. J Pharmacol Exp Ther, 310: 973-980.

**Papp L**, Vizi ES, Sperlágh B. (2004) Lack of ATP-evoked GABA and glutamate release in the hippocampus of P2X7 receptor -/- mice. Neuroreport, 15: 2387-2392.

**L Papp**, E. Sylvester Vizi and B Sperlágh. (2007) P2X7 receptor mediated phosphorylation of p38MAP kinase in the hippocampus. Biochem Biophys Res Commun, 355 (2): 568-74.

**Posters**

Beáta Sperlágh, **Lilla Papp**, Tamás Balázsa, Attila Kőfalvi, Ferenc Erdélyi, Gábor Szabó, E. Sylvester Vizi Regulation of tritiated NA release from rat hippocampal slices by presynaptic P2X-receptors. Medicinal Chemistry and Pharmacology of Purinergic Receptors, Camerino, 2003.

Sperlágh B., Kőfalvi A., **Papp L.,** Baranyi M., Deuchars J., Atkinson L., Vizi E.S. Involvement of P2X receptors in the modulation of excitatory neurotransmission in the hippocampus. Sixth IBRO World Congress of Neuroscience, Prága, 2003.

**Lilla Papp,** Tamás Balázsa, Attila Kőfalvi, Ferenc Erdélyi, Gábor Szabó, E. Sylvester Vizi and Beáta Sperlágh, Regulation of tritiated NA release from rat hippocampal slices by presynaptic P2X-receptors. Congress of Experimental and Clinical Pharmacology, Debrecen, 2003. FENS, Lisbon, 2004. EPHAR, Porto, 2004.

**Papp L,** Vizi ES, Sperlágh B. Lack of ATP-evoked GABA and glutamate release in the hippocampus of P2X7 receptor -/- mice. APHAR, Vienna, 2004. Central and Peripheral Synaptic Transmission, Varna, Bulgaria, 2005.

A. Heinrich, **L. Papp,** E. S. Vizi and B. Sperlágh. Dual modulation of [3H]noradrenaline release from the spinal cord by P2 purine receptors. Experimental Pharmacology Symposium, Budapest, 2005.

Cecília Csölle, Attila Heinrich, **Lilla Papp**, E. Sylvester Vizi and Beáta Sperlágh. P2 - receptor mediated modulation of noradrenaline release in response to stimulation of electrical field and ischemic conditions in superfused rat hippocampal slices. XI. Meeting of the Hungarian Neuroscience Society, Szeged, 2007.

Attila Heinrich, Cecília Csölle, **Lilla Papp**, E. Sylvester Vizi and Beáta Sperlágh. Dual modulation of tritiated glutamate release from the spinal cord by P2 purine receptors. XI. Meeting of the Hungarian Neuroscience Society, Szeged, 2007.