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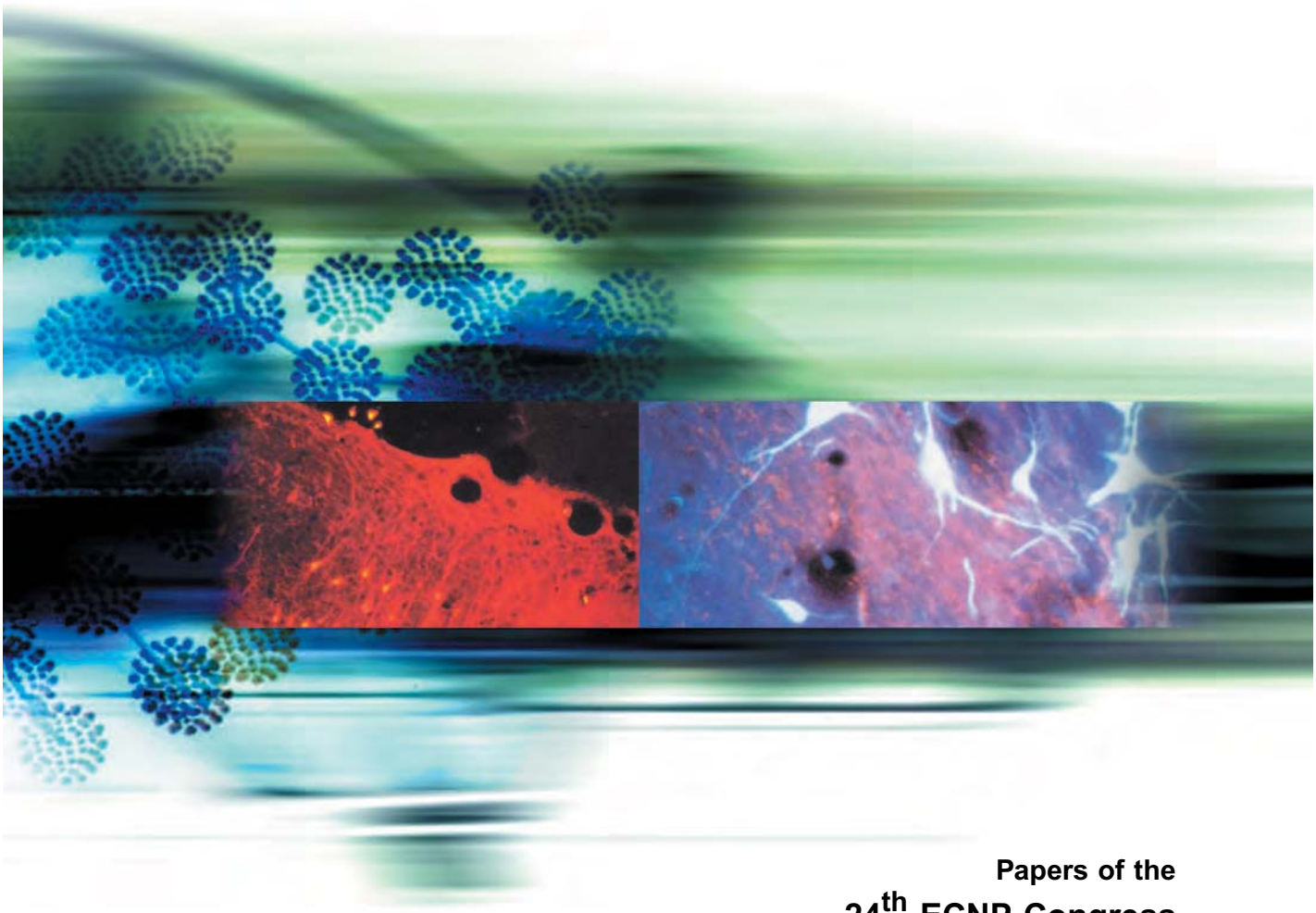

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24th ECNP Congress
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P.1.c.059 The MDR1 C3435T polymorphism and valproic acid plasmatic level in Romanian epileptic patients

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Introduction: The ATP-dependent drug transporter proteins and P-glycoprotein (Pgp) are known to be involved in drug efflux that reduces drug accumulation into cells. P-gp is a protein encoded by a small gene family, which includes 2 genes in human, MDR1 (ABCB1) and MDR2 (ABCB4), located on chromosome 7. The polymorphisms of the MDR1 gene affect the P-gp expression and function. There were described four type of MDR1 polymorphism: C3435T, C129G, G2677A and G2677T. C3435T polymorphism is associated with a lower expression of P-gp. There is an inverse relationship between CC genotype presence and brain protection confered by P-gp [1]. Some studies revealed that MDR1 gene polymorphisms could influence drugs plasmatic levels [2], while others did not confirm this observations [3].

Aim: The aim of the study was to evaluate the influence of MDR1 C3435T polymorphisms on the bioavailability of valproic acid (VPA) and the correlation between the genotype and the plasma levels.

Materials and Method: 60 patients with epilepsy, with a mean age of 37.15±12.76, evaluated in the Neurology Clinic of Cluj-Napoca, Romania, were included into the study. All patients were under stable treatment with valproic acid for at least a month. Steady state plasma concentrations of VPA were determined using the GC/FID technique, using an Agilent 6890N GC system. We considered therapeutic level of VPA between 50–100 μg/mL. According to steady-state plasma concentration of VPA the patients were divided into three groups: patients with sub-therapeutic (<50 μg/mL), supra-therapeutic (>100 μg/mL) or normal (50–100 μg/mL) therapeutic levels. Genotyping was conducted using DNA extracted from lymphocytes of peripheral blood Using the PCR-RFLP method for each patient we have determined allelic variant of MDR1 C3435T polymorphism. Three genotype of MDR1 C3435T polymorphism were identified: CC, CT and TT. We correlated the plasmatic level of VPA with the wild or mutant genotype of MDR1 gene. The statistical evaluation was performed using SPSS version 17, with a significance at $p < 0.05$.

Results: 36.7% were male patients and 63.3% female patients, sex ratio was M:F = 0.58. 55% of the patients presented idiopathic epilepsy, while 45% of them had a secondary form of the disease. The mean plasmatic level of VPA was 72.47±26.92 μg/mL. 71.7% of the patients had therapeutic level of valproic acid, 13.3% supra-therapeutic and 15% sub-therapeutic level of VPA. 13.3% of the patients present CC genotype, while 58.3% present CT genotype and 28.3% TT genotype. The mean VPA plasmatic level is lower in patients with CC genotype (59.14±17.89), but with no significance ($p = 0.314$), compared with TT (77.07±26.32) and CT genotypes (73.78±28.56).

Conclusions: There was no significant correlation established between the presence of C3435T polymorphism and sub or supra-therapeutic level of valproic acid. The polymorphism of MDR1 gene has no influence on the valproic acid serum level.

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P.1.c.060 (±)3,4-Methylenedioxyamphetamine inhibits a TEA-sensitive potassium current in the hippocampus

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Purpose: The amphetamine-based designer drugs include (±)3,4-methylenedioxyamphetamine (MDA; known as the 'love drug'), (±)3,4-methylenedioxymethamphetamine (MDMA), and N-ethyl-3,4-methylene-dioxyamphetamine (MDEA), all of which are widely abused psychotropic drugs [1]. High doses of MDMA and MDA also induce seizures in animals and humans [2]. The mechanism remains unclear and different mechanisms of toxicity may exist among amphetamine analogs. In our previous studies, MDA was found to elicit in vitro bursting firing of action potentials in the central RP4 neuron of the African snail, Achatina fulica Ferussac [3]. The present study aims to investigate the effects of the ring-substituted analog of amphetamine, i.e. MDA, on the electrophysiological behavior of hippocampal CA1 neuron.

Methods: The effects of MDA were studied in hippocampal CA1 neuron of neonatal rats, using the whole-cell patch-clamp method. Experiments were carried out using hippocampus or cortex slices obtained from 5- to 10-day-old Sprague Dawley rats. After rats were anaesthetized with ether and decapitated, the brains were removed. A block of tissue containing the hippocampus was separated from the brain and glued to the cutting chamber of a tissue slicer with cyanoacrylate glue. The chamber was filled with ice cold artificial cerebrospinal fluid (aCSF) gassed with O_2 and 300 μm thick slices were prepared. The slices were transferred to an incubation chamber in aCSF and were incubated for at least 1 hour at room temperature under continuous oxygenation.

After incubation, the slice was placed in a glass-bottomed recording chamber (volume of about 0.7 ml) fixed to a microscope stage. The slice was immobilized by pressing onto the bottom of the recording chamber with a specially fabricated grid of nylon threads attached to a U-shaped platinum frame. Solutions of various ionic compositions and drugs will be applied by switching the perfusion fluid. Hippocampal neurons were viewed

using an upright microscope with a water-immersion objective lens. Conventional patch pipettes were made from standard-wall glass capillaries. The pipette tip has an orifice of 1–2 mm and DC resistance of 4–6 M Ohm when filled with standard pipette solution. Whole-cell currents will be recorded with a Multiclamp 700B amplifier. Cells will be located and patched under visual control. A gigaohm seal (> 10 G omega) will be established in the cell-attached mode prior to perforation of the patch membrane for whole-cell recording.

Summary of results: Extracellular application of MDA (30 μM) increased excitability of hippocampal CA1 neurons. In some CA1 neurons, MDA elicited action potential bursts. MDA at 30 and 100 μM decreased the total outward current. TEA (30 mM) decreased the total outward current. However, MDA did not decrease the total outward current in the presence of TEA (30 mM). MDA at 30 and 100 μM did not affect the fast-inactivating K^+ current (I_A) current. TEA at 30 mM elicited action potential bursts in the hippocampal CA1 neuron.

Conclusions: These results suggest that MDA increases the excitability of CA1 neuron and this effect is closely related to a TEA-sensitive potassium current.

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P.1.c.061 Changes in hippocampal plasticity and neurogenesis during pregnancy and post partum are reversed by offspring separation

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Pregnancy, delivery and the post partum period are among the most important physiological condition in which the brain of female undergo to the greatest functional and morphological modification needed to adapt the behavior to the onset of motherhood. The changes in the property of neurons such as altered neuronal excitability, in the synthesis and release of different neurotrasmitters, neuropeptides and hormones observed during pregnancy and/or the onset of maternal behavior are selectively associated to functional and morphological modifications of specific neuronal population. Given the differential dramatic changes in the plasma and brain content of hormones are associated to pregnancy, delivery and the post partum period, several studies have been conducted to clarify whether the temporal association between hormone fluctuation during these physiological conditions have also a correlation with the functional and morphological changes of neuron observed in specific brain areas during those conditions and the associated behavior. Brain Derived Neurotrophic Factor (BDNF) belongs to a family of secretory proteins, the neurotrophins. These proteins initiate their biological functions by interacting with specific receptors. BDNF is a key mediator of neuronal plasticity, regulates synaptic composition, neurotransmitter release and neuronal excitability in the adult nervous system. Long term action of BDNF plays a key role in learning and memory, emotional and affective behavior [1]. BDNF is involved in the regulation of long-term plastic changes of glutamatergic and GABAergic synapses and has been shown to facilitate long-term synaptic potentiation (LTP) in synapses of adult rats. Long-term application of BDNF exerts a complex modulatory action on dendritic and axonal growth in the brain [2]. Activity-regulated cytoskeleton-associated protein (Arc) plays a relevant role in synaptic plasticity. It is rapidly induced by synaptic stimulation and is localized in dendritic spines of different neuronal populations. A role for BDNF-Arc signalling in the regulation of neuronal architecture has been clearly demonstrated [3]. In the present study the amount of BDNF and Arc, dendritic spines density (DSD), LTP and neurogenesis was measured in hippocampus of female rats during pregnancy and after delivery. The same parameters were also evaluated after delivery in the mothers deprived of their pups one week after birth. BDNF, Arc and DSD started to be markedly increased in the late of pregnancy, an effect that lasted for a least 21 days after delivery. In the dentate gyrus, the increase in DSD, BDNF and Arc expression, evident in the late pregnancy and during lactation, was associated to a significant increase of LTP and a dramatic reduction of neurosteroid content compared to control rats. In contrast was observed an increase of neurogenesis in the late pregnancy and a reduction during lactation. Finally, stress due to the separation of pups from their dams induced a marked reduction of DSD, BDNF and Arc protein, the amounts of which felt at values markedly lower than control. The motherhood-induced change in the amount of DSD, BDNF, Arc, LTP and neurogenesis as well as the reversal by pups separation suggest a crucial role of neuronal plasticity in the regulation of rat maternal care.

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P.1.c.062 Importance of targeting mitochondria in the search for new neuroprotectors

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The majority of adult-onset neurodegenerative disease is characterized by progressive death of specific classes of neurons. For most of these diseases the cause is unknown, so there exist no validated molecular targets and there are no therapies that can slow or cure these devastating diseases. However, an extensive body of evidence suggests that they share a common pathogenic mechanism that includes oxidative stress, excitotoxicity, mitochondrial dysfunction, protein aggregation, axonal transport defects, and inflammatory cascades, and that aging is the main risk factor for these diseases.

Mitochondrial abnormalities have long been implicated in the aging process, but only recently has their influence been extended to neurodegenerative diseases. Specifically, mitochondria