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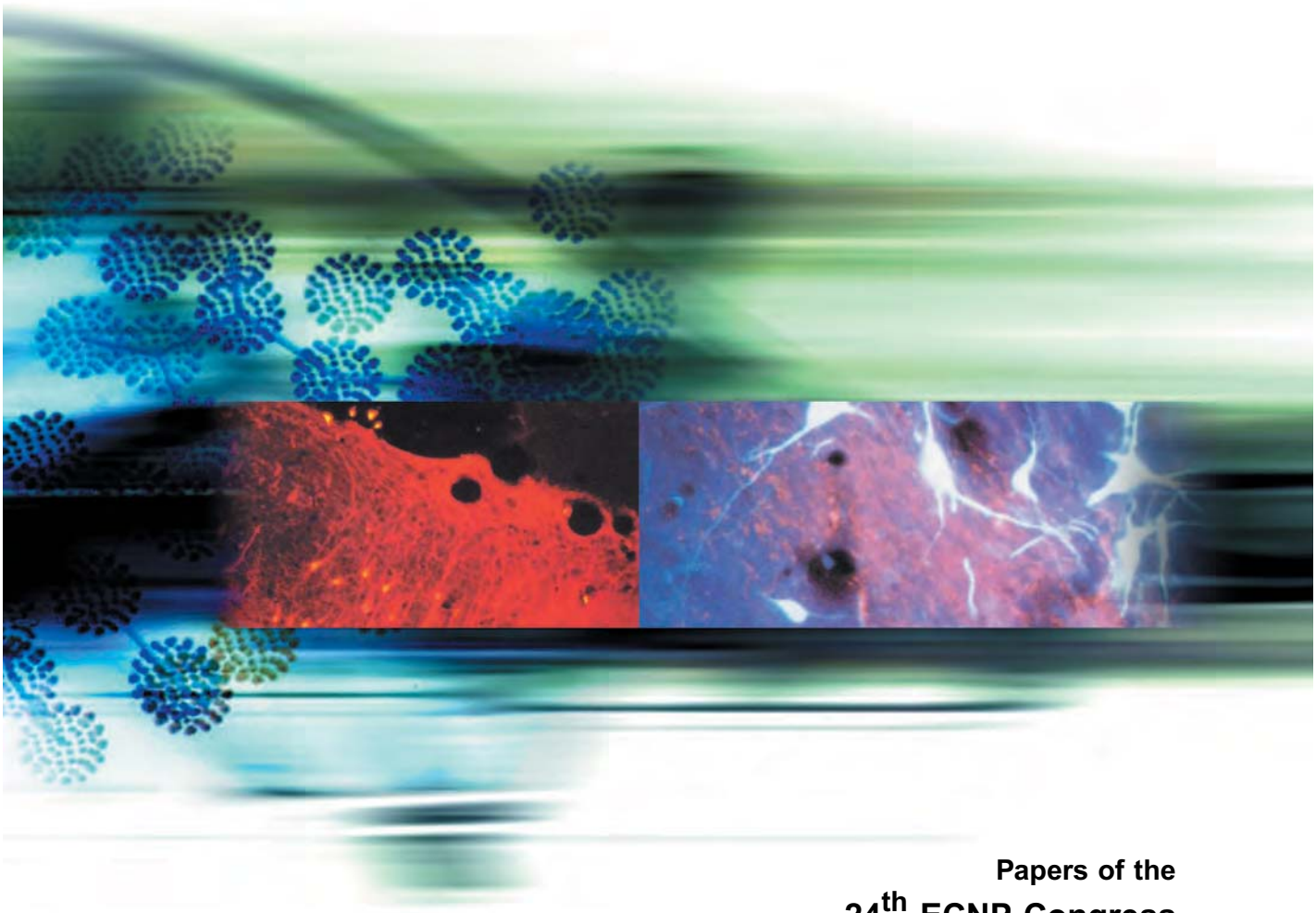

Papers of the
24th ECNP Congress
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– regulation of gene expression;
– various neuroprotection effects, influence on neurogenesis, or antioxidant action of the lithium ion.

It has been reported that lithium inhibits lipid peroxidation and protein oxidation. It was also stated that lithium salts stimulate proliferation of different cell types, increase neurogenesis (especially in the hippocampus), and delay cell death induced by various factors like ischemia, oxidative stress or glutamate exitotoxicity [1].

Oxidative stress is a state of imbalance between oxidant processes and antioxidant defence. It probably plays an important role in the pathophysiology and the course of bipolar disorder. Many studies have shown that patients with bipolar disorder have increased lipid peroxidation, not only during acute episodes but also during remission [2]. This supports that oxidative damage might persist during and after the illness.

Aim of the study: The aim of this research is to estimate the influence of lithium (alone and in combination with haloperidol) on oxidative stress parameters in human plasma (in vitro) and the effect of these substances on oxidant–antioxidant balance and viability of neuronal cell lines.

Materials and Methods: Evaluated oxidative stress parameters are: lipid peroxidation and total antioxidant status. Lipid peroxidation is measured by the concentration of thiobarbituric acid reactive substances (TBARs) (method of Rice-Evans). Measurement of total antioxidant capacity is done as a decolorization assay with the pre-formed radical monocation of 2,2′-azinobis-(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS·+) (method of Re).

Plasma samples were taken from 58 healthy volunteers who did not have any psychiatric or physical disorders, head injuries in the past, allergy, disorders of lipid or carbohydrate metabolism, or any pharmacological treatment, and were non-smokers. Experimental samples were incubated with different drug concentrations; control samples were prepared without drugs.

Cell lines used were human neuronal cell cultures – neuroblastoma SH-SY-5Y. Viability and oxidative stress parameters were measured in pure samples, samples with lithium alone and samples with lithium plus haloperidol. Viability was measured using MTT test, lipid peroxidation with the Rice-Evans method and total antioxidant status with the Re method.

Results: Statistically significant increases of TBARs level were observed during the incubation of plasma with the combination of lithium (both prophylactic and therapeutic concentrations) and haloperidol compared to control values ($p < 0.05$). Incubation of plasma with lithium or haloperidol alone did not cause statistically significant changes in TBARs level. There was no effect of lithium and haloperidol alone or in combination on neuroblastoma cell viability in vitro.

Summary: The study showed that a combination of haloperidol and lithium, but not either drug alone, induces a significant increase in lipid peroxidation in human plasma in vitro. These results suggest that oxidative stress may play a role in this combination toxicity.

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P.1.c.020 Memantine elicits action potential bursts in the central snail neuron

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Purpose of the Study: Memantine is a derivative of amantadine used in clinical practice to treat several neurological disorders associated with excitotoxic cell death, including Parkinson's disease, amyotrophic lateral sclerosis, Alzheimer's disease, epilepsy, stroke, spasticity, convulsions, and vascular dementia [1]. Fast series of action potentials, typically referred to as "bursts" are observed in various neuronal types in the central nervous system. Several lines of evidence indicate that the bursts have special importance in brain function. It have been reported that memantine induced action potential bursts in dopamine neurons of substantia nigra pars compacta in rats [2]. However, the mechanism underlying the action potential bursts remains unclear. This study sought to determine the effects of the memantine-elicited action potential pattern changes in the central snail neuron.

Methods: Experiments were performed on identified RP4 neuron from the subesophageal ganglia of the African snail Achatina fulica Ferussac. The ganglia were pinned to the bottom of a sylgard-coated perfusion chamber and freed from the connective tissue sheath to allow easy identification and penetration by microelectrodes. Intracellular recordings were made with a Gene clamp 500 amplifier (Axon Instrument Co.). The ionic currents of the central snail neurons were measured by the two-electrode voltage clamping method. Two microelectrodes were penetrated into the neuron. The recording electrode (5–6 MΩ) and the current electrode (1–5 MΩ) were filled with 3M KCl. All potentials and currents were recorded on tape by a digitalizing unit (Digidata 1322A) and analyzed.

Summary of Results: The control RP4 neuron exhibited spontaneous regular firing of action potentials. Extracellular application of memantine at 100 μM did not alter the action potential firing pattern of the RP4 neuron. However, extracellular application of memantine at 300 μM or higher concentrations elicited action potential bursts in the RP4 neuron. The memantine-elicited action potential bursts were not affected by Ca^{2+}-free solution and high-Mg^{2+} solution (30 mM). Further, the memantine-elicited action potential bursts were affected neither by pretreatment of the protein kinase A inhibitor, KT-5720 (10 μM) nor by the protein kinase C inhibitor, Ro 31–8220 (20 μM). In the voltage-clamp study, memantine at 300 μM decreased the total inward currents, the delayed rectifying current (I_{KD}) and the fast-inactivating K^+ current (I_A). Application of 4-aminopyridine (4-AP), an inhibitor of I_A, failed to elicit action potential bursts, whereas tetraethylammonium chloride (TEA), an I_{KD} blocker, successfully elicited action potential bursts [3]. At a lower concentration of 5 mM, TEA facilitated the induction of action potential bursts elicited by memantine.

Conclusion: It is concluded that the memantine-elicited action potential bursts may not due to synaptic effects of neurontransmitters. Further, the memantine-elicited bursts are not related to protein kinase A and protein kinase C signaling pathways of the RP4 neuron. However, the memantine-elicited bursts may be associated with the inhibition of TEA-sensitive I_{KD} current.

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P.1.c.021 Effect of phosphodiesterase 2A inhibition on striatal dopamine in a microdialysis study and its reflection in dopamine-associated effects in animal models

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Purpose: Phosphodiesterases (PDE) are expressed in nearly all mammalian cells. They catalyze the degradation of cAMP and/or cGMP and are thus key regulators of intracellular cyclic nucleotide levels. As a consequence, they may play an important role in numerous physiological and pathophysiological processes.

PDE2A hydrolyses both cAMP and cGMP and is activated upon cGMP binding to its N-terminal GAF-B domain. It is highly expressed in different brain areas, i.e. cortex, hippocampus and striatum. Only a few PDE2 inhibitors have been pharmacologically characterised so far (BAY60–7550, ND-7001) suggesting their pro-cognitive and anxiolytic potential (1, 2). However, little is known regarding the effect of PDE2A inhibitors on the different neurotransmitter systems in the brain that may underlie such efficacy.

In the present study, the effect of PDE2A inhibition on striatal dopamine and its metabolite 3,4-dihydroxyphenylacetic acid (dopac) was investigated in microdialysis. Additionally, the influence of several PDE2 inhibitors on dopamine-associated pharmacological effects was investigated.

Methods: The effect of PDE2A inhibition on extracellular dopamine and dopac in the striatum was evaluated by microdialysis. A microdialysis probe (CMA/12, membrane length 4 mm) was inserted via guide cannula (AP +1.0, L –3.0, V +5.5) into the striatum. Probe was perfused with aCSF at a flow rate of 1 µl/min that allowed for the collection of 20 µl samples every 20 minutes into microvials. Samples were measured by HPLC and electrochemical detection. Additionally, the effect of several PDE2A inhibitors on reserpine-induced hypothermia in mice and on haloperidol-induced catalepsy in rats has been tested. To examine whether the effect of the PDE2A inhibition is CNS mediated, the effect of intrastriatal compound administration on haloperidol-induced catalepsy was also evaluated, using BAY60–7550 as a reference compound.

Results: The PDE2A inhibitor BCR840 at 10 mg/kg po significantly reduced extracellular dopamine and dopac levels in the striatum. BAY60–7550 at 30 mg/kg po significantly decreased extracellular dopac and slightly reduced extracellular dopamine in the striatum of rats. At the same doses both compounds significantly reversed reserpine-induced hypothermia and haloperidol induced catalepsy indicating an activating effect on the dopamine neurotransmitter system. Further confidence in the underlying mechanism of action was obtained from further PDE2A inhibitors being orally and dose-dependently active in these models. BCR909 significantly reversed haloperidol induced catalepsy starting at 10 mg/kg after oral dosing. When injected intrastriatally, the administration of 1 and 10 µM (1 µl administration volume) BCR909 resulted in a significant and dose dependent inhibition of haloperidol induced cataleptic behaviour. This indicates that the PDE2A inhibitory effect in the described models was CNS mediated.

Conclusions: This study indicates that PDE2A inhibition has a modulating effect on the dopamine neurotransmitter system. PDE2A inhibitors significantly reduced extracellular dopamine and dopac in the striatum of rats and reversed reserpine induced hypothermia and haloperidol induced catalepsy. The data indicate that the effects of PDE2A inhibitors are centrally-evoked and may be at least partially mediated by a modulation of the dopamine neurotransmitter system.

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P.1.c.022 Effects of 3,4-methylenedioxymethamphetamine (MDMA or ecstasy) on prosocial feelings and oxytocin plasma levels in humans

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Background: The recreationally abused drug ±3,4-methylenedioxymethamphetamine (MDMA, ecstasy) is reputed to produce strong psychological effects such as increased prosocial feelings and feelings of closeness to others. These effects of possibly elevated empathy also led to the suggested classification of MDMA and related compounds into a drug class called "entactogens". Animal studies have shown a key role for the neuropeptide oxytocin in the regulation of social cognition and prosocial behavior. MDMA increases prosocial behavior in rodents, an effect which is attenuated by an oxytocin receptor antagonist. A recent human study showed that oxytocin improved the ability to infer affective mental states of others from facial cues in a 'mind reading' task possibly facilitating social approach behavior. We hypothesized that MDMA would increase oxytocin plasma levels and thereby also improve performance in the 'mind reading' task in humans.

Objective: The aim of this study was to investigate effects of MDMA on oxytocin plasma levels, prosocial feelings, and 'mind reading' in healthy volunteers.

Methods: We assessed the effects of MDMA on oxytocin plasma levels, subjective effects, and on a 'mind reading' task in 16 drug-naïve healthy subjects using a double-blind, placebo-controlled, within-subject design. Oxytocin plasma levels were assessed at baseline and 120 min after placebo or MDMA. Subjective effects were repeatedly measured by Visual Analogue Scales (VAS) and an Adjective Mood Rating Scale. A computerized version of the Reading the Mind in the Eyes-Revised test (RMET) was applied to assess the subjects ability to identify complex emotions from 36 pictures of the eye regions of different men and