irreversible inhibition of MAO B by deprenyl both in vitro and in vivo. H. caused induction of aromatic-L-amino-acid decarboxylase mRNA expression and both inhibition of dopamine transporter (DAT) and MAOB mRNA (PT-PCR method). Using patch-clamp method H. was shown to be a noncompetitive inhibitor of NMDA-receptor channels with $IC_{50}$ about 12 μM. H. had moderate antiradical activity. H. was characterized as immunotropic agent with prolonged action upon several parameters of immunity including antiinflammatory effect.

No adverse effects of H. were revealed. H. did not alter learning and memory, had no sedative, no stimulatory effect, no addictive potential. Antidepressant and anxiolytic action of H. was demonstrated in some animal models.

Thus, H. was effective with in vivo models of parkinsonism. Several components of the mechanism of action have been identified for H. up to now which can contribute to its antiparkinsonian and neuroprotective activity. Clinical trials of H. are planned in the nearest future.

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## P.5.006 Electrophysiological analysis of the hemantane effects in rats with $MPP^+$-induced parkinsonism

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The search for new antiparkinsonian drugs is a highly actual problem taking into account the spreading of Parkinson's disease and the lack of effective and safe pharmacotherapeutic agents. Hemantane – N-2-adamantyl hexamethylenimine hydrochloride – is a novel potential antiparkinsonian drug developed at the Institute of Pharmacology RAMS. Effects of hemantane upon the behavior and bioelectrical activity of brain structures were assessed in rats with parkinsonian syndrome induced by intranigral injection of 1-methyl-4-phenyl pyridinium ion ($MPP^+$). During the surgery electrodes were implanted in sensorimotor cortex, nucleus caudatus and substantia nigra, bilaterally. Hemantane (10 mg/kg, i.p.) was administered for seven days after the surgery. The motor activity, extrapyramidal symptoms and bioelectrical activity in brain structures were registered on days 1, 3, 5 and 7 after the surgery. The electrophysiological EEG parameters assessed included power spectrum, coherence and the leading structure. The data were estimated by one-side Student's t-criterion. Hemantane effectively relieved parkinsonian symptoms, decreased number and duration of paroxysmal activity charges, increased power spectrum at beta-waves, decreased coherence and changed the leading structure. Hemantane effect was more pronounced after subchronic administration. In this experimental model it was similar to that obtained in previous experiments on the model of MPTP-induced parkinsonian syndrome [1]. Thus, hemantane was effective on several models of parkinsonism and it is expected to have certain activity in clinical trials.

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## P.5.007 Perspectives of the use of a new antioxidant mexidol in the treatment of Parkinson's disease

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Oxidative stress plays a pivotal role in the development of neurodegenerative disorders. Thus drugs with antioxidant profile have perspective in the treatment of Parkinson's disease [1,2]. Mexidol (2-ethyl-6-methyl-3-hydroxypyridine succinate) has a wide spectrum of pharmacological activities: neuroprotective, antihypoxic, anxiolytic, antiatherogenic, nootropic and cardioprotective [3]. The aim of this study was to evaluate the effects of the antioxidant mexidol combined with traditional antiparkinsonian medication on the EEG power spectra and coherence (Coh). 12 patients with Parkinson's disease have been involved in this study. All patients were treated with mexidol (250 mg intravenously) daily in the morning during 10 days. 7 patients were taking levodopa-containing medicine – madopar (mean daily dosage 500 mg), 5 patients – amantadine sulfate (PK-Merz, mean daily dosage 200 mg). Before the mexidol treatment all the patients showed different degrees of EEG disturbances: decrease in the power of alpha-1, alpha-2 band and increase of power of the beta-1, beta-2 and gamma bands.

Treatment with mexidol caused improvement of locomotor functions and memory, as well as a decrease of tremor. Correlations between the diminution of extrapyramidal symptoms and EEG parameters were revealed. In most of the patients mexidol produced a decrease in the power of beta-2 and gamma bands and visible changes of Coh index for short and long intra- and interhemispheric pairs of sites. The power of the alpha band showed different degrees of augmentation. Contrary to the standard antiparkinsonian drugs mexidol produced an intensification of power and Coh in the alpha band for most intra- and interhemispheric pairs of occipital and temporal areas; this effect suggests to be related to the neuroprotective effects of this drug.

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## P.5.008 Presynaptic interaction between rat brain dopaminergic and glutamatergic systems in the mechanism of action of the novel antiparkinsonian drug hemantane

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Hemantane (N-2-adamantyl-hexamethylenimine HCI, A-7) demonstrates pronounced anti-parkinsonian effect in experiments associated with drug inhibitory *in vitro* action on MAO-B activity and with elevation of striatal extracellular dopamine in ambulatory rat brain [2]. On the other hand, hemantane, as well as other adamantane derivatives amantadine and memantine, displays properties of NMDA-receptor blocker. Thus, this study was aimed to examine the putative influence of hemantane on synaptosomal re-uptake of [$^3$H]-DA *in vitro*.

Recently it was shown that after acute administration of tritiated Hemantane (10 and 20 mg per kilo, i.v. and p.o.) radioactivity appeared in rat brain striatal (but not in hippocampal or cerebellar) tissue during the first 1–2 h, and increased maximally ($C_{max}$ 3.3 ug per g) up to 8 h [1]. Therefore, the synaptosomes from rat brain striata in the study of the drug influence on dopamine re-uptake function were applied. Hemantane inhibited concentration-dependently synaptosomal DA uptake within 10–500 uM range, diminishing the $B_{max}$ value from 9.0 pmoles/min/mg protein to 5.1 pmoles/min/mg protein ($p < 0.05$), while the magnitude of $K_m$ was unchanged (0.5 uM in control) which is proper for non-competitive mode of action. Competitive and non-competitive antagonists of NMDA-receptors (+)-CPP and MK-801 (dizocilpine) suppressed the [$^3$H]-DA uptake with $IC_{50}$ 6 uM and 38 uM, respectively. On the contrary, only the non-NMDA-receptors agonist quisqualate at the highest concentration tested (1, 10 and 100 uM) slightly inhibited DAT (–37% to control; $p < 0.05$), while NMDA failed. Thus, the blockade of NMDA-receptors and activation of non-NMDA-receptors (e.g. mGluR types) resulted in DA transporter inhibition.

In order to investigate the role of protein–lipid interaction in brain synaptosomal membranes the *in vitro* effects of NMDA- and non-NMDA-agonists on bulk and annular membrane lipid microviscosity using fluorescent probe Pyrene were examined. Both the NMDA and quisqualate ($10^{-7}$–$10^{-4}$ M) moderately (+16–18% to control; $p < 0.05$) increased the viscosity of membrane bulk lipids, while that of annular lipids failed. These data suggest that modulatory influence of glutamate receptors on DA transporter activity may be transmitted via regulation of membrane fluidity even without any changes of DAT expression. This hypothesis does not exclude the possible involvement in DAT modulation of various intracellular messengers like cAMP, $Ca^{2+}$, DAG, IP3, as well as PKA and PKC.

Thus, the mechanism of striatal DA-ergic efficacy amplification evoked by hemantane, a NMDA-receptor ligand with low affinity, may include the non-competitive inhibition of DAT realized by membrane lipids and/or intracellular second and third messengers.

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