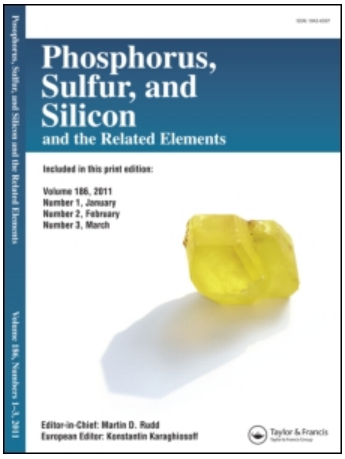

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Mechanism of Action of Phosphorylacetic Acid Hydrazides as Memory Enhancers and Neuroptotectors

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Introduction

Dementias and amnesias as the result of neurodegenerative diseases or continious ischemia of brain are now recognised as a major problem and affect a significant proportion of the elderly population. The pharmacological treatment of dementia is directed primaraly at correction of neurotransmitter deficits or enchancement of cerebral metabolic activity, but options are limited at present, because neurochemical pathology of dementias also include a disrupted regulation of neurotransmitter systems-signal transduction mechanism, which depends on cell's membranes conditions.

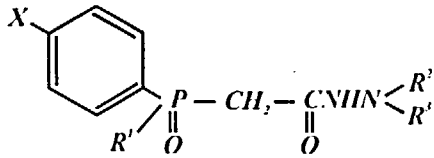
The aim of this work is the study of mechanism of action of phosphoryacetic acid hydrazides (Fig.1) as novel class of compounds for treatment dementias. We have shown recently that they possess significant neuroprotective, memory enhancing and antidepressive activities [1,2].

Results and discussion

In experiments in vitro the most active compounds (chloroetoxyphenylphosphenylacetic hydrazides) have affinity for the glycine stryhnineinsensitive site of NMDA-receptor and haven't affinity for other receptors of excitatory amino acids (NMDA, AMPA, kainate, MK-801 site).

On the model of hypobaric hypoxia on mice these compounds given i.p. and orally, reinforce neuroprotective action of ketamine, the noncompetitive antagonist of NMDA- receptors, by increasing the time of survival in the chamber (Fig. 2), so we can propose their antagonistic influence on glycine site of NMDA-receptors.

Analysis of structure-activity relationships shows that affinity depends on substituents of both phosphoryl and hydrazide fragment in the molecule, but the



X=(CH$_3$)$_2$N, R=ClCH$_2$CH$_2$O, R'=R''=H (1)
X=CH$_3$, R'=ClCH$_2$CH$_2$O, R=R''=H (2)
X=Cl, R=ClCH$_2$CH$_2$O, R'=R=H (3)
X=(CH$_3$)$_2$N, R=ClCH$_2$CH$_2$O, R=H, R'=C(O)CH$_3$ (4)
X=(CH$_3$)$_2$N, R=ClCH$_2$CH$_2$O, R'=H, R=CH(OH)CCl$_3$ (5)
X=(CH$_3$)$_2$N, R=ClCH$_2$CH$_2$O, R',R''=CHC$_6$H$_4$COOH (6)
X=(CH$_3$)$_2$N, R=ClCH$_2$CH$_2$O, R',R''=CHC$_6$H$_4$ (7)
X=H, R=CH$_3$, R'=R''=H (8)
X=(CH$_3$)$_2$N, R=OC$_6$H$_5$, R'=R''=H (9)
X=(CH$_3$)$_2$N, R=ClCH$_2$CH$_2$O, R', R''=C(CH$_3$)$_2$COOH (10)
X=(CH$_3$)$_2$N, R=ClCH$_2$CH$_2$O, R=R''=H (HCl) (11)
X=H, R=CH$_3$, R=R''=H (HCl) (12)
X=H, R=C$_6$H$_5$, R', R''=CHC$_6$H$_4$ (13)

Fig. 1. Phosphotylacetic acid hydrazide.

phosphoryl fragment, especially with phenyl radical, has priority for this activity. Thus, administration of diphenylphosphinylacetic acid together with ketamine reinforces neuroprotective action while diethylphosphinylacetohydrazide doesn't influence it. The substitution of chloroetoxy radical of phosphoryl fragment by ethyl radical doesn't influence neuroprotective effect of ketamine too. The substitution in phenyl radical of phosphoryl fragment changes the affinity to glycine site. Thus, substitution of dimethylamino group of compound (1) by chloride atom (3) enhances binding, which is associated, probably, with lipophility. The substitution in hydrazide fragment influences the affinity too, but in a less marked form.

All compounds (especially unsubtitued hydrazides and hydrazons) have antioxidant activity in vitro, reducing concentration of malonic dialdehyde (Fig.3). Diphenylphoshinylacetic acid doesn't show antioxidant activity. The presence of phenyl radicals in phoshoryl fragment reduces antioxidant properties (8 and 15). Notably, HCL-salts of CAPAH and diphenylphosphinylacetohydrazide were as active as hydrazones.

Chloroetoxyphenylphoshenylacetohydrazides, espesially with unsubstituted hydrazide group, have significant membrane-stabilising activity, reducing osmotic haemolysis of erythrocytes. Substitution of chloroetoxyradical in phosphoryl fragment by ethyl or aryl decreases this activity.

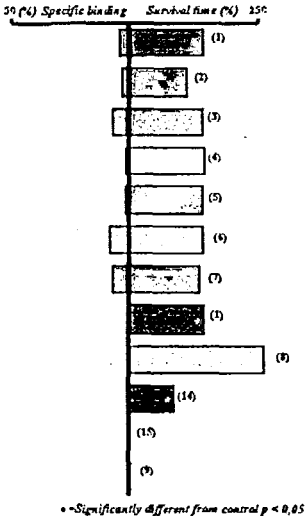


Fig. 2. The influence of phosphorylacetic acid hydrazides on neuroprotective effect of ketamine and affinity to glycine site of NMDA-receptor

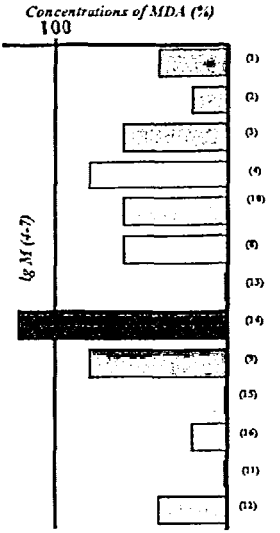


Fig. 3. The influence of phosphorylacetic acid hydrazides on concentration of malonic dialdehyde

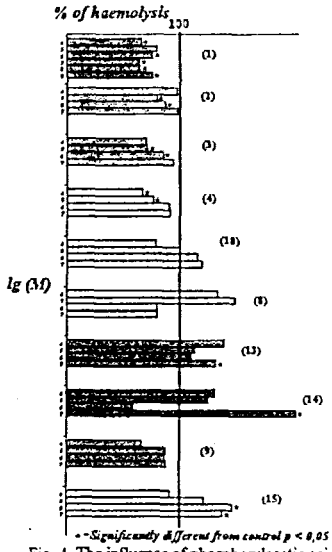


Fig. 4. The influence of phosphorylacetic acid hydrazides on osmotic haemolysis of erythrocytes

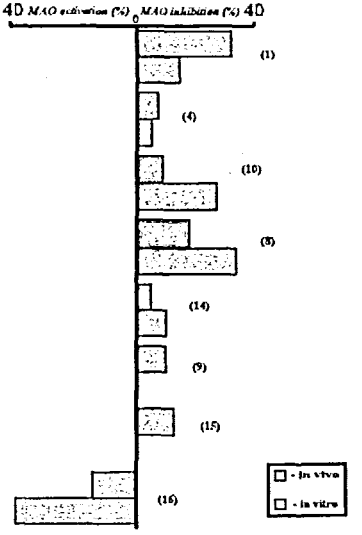


Fig.5. The influence of phosphorylacetic acid hydrazides on activity MAO B in vivo and in vitro

The influence of phosphorylacetic acid hydrazides on activity MAO B was studied in vivo and in vitro in homogenates of the brain of rats and mice. All phosphorylacetic acid hydrazides are inhibitors of MAO B (substrate; benzylamine). MAO-inhibition activity depends not only on the presence of hydrazide group but on the area of phosphoryl fragment too. The activity of diethylphoshinylacetic hydrazide and diphenylphosphinylacetic acid separatly is less marked. The combination of diethylphoshinylacetic acid with hydrazide group is most active. Substituted hydrazides are less active than unsubstituted ones and hydrazones. The replacement of hydrazide group by amide group contributes to disappearence of MAO-inhibition activity.

Conclusion

The results of these investigations have shown that phosphorylacetic acid hydrazides have a complex of mechanisms influencing the different links of pathological process in dementias and can be effective for the treatment of this pathologies. Besides these results are of importace for medicinal chemistry because they allow to design further molecules with affinity to the glycine site, antioxidant and MAO-inhibition activities, which freely penetrate the blood-brain barrier.

These studies have defined the chemical structure which is optimum and based on the combination of phosphoryl fragment with phenyl, chloroethoxic radicals and hydraide group - 2-chloroethoxy 4-dimethyl aminophenylphosphinylacetohydrazide (CAPAH).

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