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Research paper

Effects of memantine and its metabolite Mrz 2/373 on soman-induced inhibition of acetylcholinesterase *in vitro*

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ABSTRACT

Memantine is the non-competitive *N*-methyl-D-aspartate (NMDA) receptor antagonist, used in the treatment of Alzheimer's disease. It is also known that memantine pretreatment assured protection of skeletal muscles from poisoning with nerve agents and an interaction between memantine and AChE was proposed. In the study presented we examined interactions of memantine and its main metabolite (1-amino-3-hydroxymethyl-5-methyl adamantine, Mrz 2/373) with AChE *in vitro* as well as their effect on kinetics of the soman-induced AChE inhibition and aging. The results have shown that memantine and Mrz 2/373 exerted concentration-dependent inhibition of AChE, with Mrz 2/373 being a more potent inhibitor than the parent compound. Addition of soman 7.5 nmol/l induced gradual AChE inhibition that became almost complete after 20 min. Memantine (0.1, 0.5 and 1 mmol/l) and Mrz 2/373 (0.1, 0.5 and 1 mmol/l) concentration-dependently slowed down the AChE inhibition. After 30 min of incubation of AChE with soman, 5 min of aging and 20 min of reactivation by asoxime (HI-6 dichloride), AChE activity was 8.1% in control medium, 30.7% and 41.9% after addition of 1 and 10 mmol/l memantine, and 16.1% after addition of 1 mmol/l Mrz 2/373. It was concluded that it is possible that memantine and Mrz 2/373 can prevent AChE from inhibition by soman, which could, along with known memantine's neuroprotective activity, explain its potent antidotal effect in soman poisoning. The potential effect on aging of the soman-AChE complex warrants further studies.

1. Introduction

Poisonings with organophosphorus (OP) have been over decades a serious therapeutic problem [1–3]. This is especially true for the nerve agents (tabun, sarin, VX) that were used in several regional armed conflicts [4,5], but also by some terrorists [6–10]. Among them, soman (1,2,2-trimethylpropylmethylphosphonofluoridate) remains the most difficult one to treat, due to a very short aging rate of the soman-acetylcholinesterase (AChE) complex that makes it resistant to reactivation by oximes [11–13]. General resistance of this complex to most of the available oximes occurs even if they were administered timely [12,14]. In addition to this, soman intoxication is accompanied by early occurrence of convulsions (Misulis et al., 1987 [15]; and central respiratory paralysis [16,17].

Several dozens of antidotes were tried in experimental settings to treat OP-induced toxic and lethal effects of soman and other nerve agents, with more or less success [18–20]. Besides classical post-exposure antidotes, like atropine and other anticholinergics [21, 22] and pralidoxime, obidoxime, trimedoxime, asoxime (HI-6 dichloride) and other H- [14,23–25] and K-oximes [26–30] and diazepam and other anticonvulsants [31–33], pre-treatment antidotes were also investigated [20]. Among them, most attention was paid to carbamate, e.g. physostigmine and pyridostigmine [34,35] and non-carbamate (e.g. huperzine) reversible AChE inhibitors [36,37].

Adamantanes also emerged as a class of potential prophylactic antidotes against intoxication with nerve agents (McLean et al., 1986; [38]; and OP or carbamate pesticides [39–41]. The *in vivo* studies with one of them, memantine (1-amino-3,5-dimethyladamantane, Mrz 2/145), were especially encouraging, suggesting that this non-competitive antagonist of *N*-methyl-D-aspartate (NMDA) receptors, could protect rodents from death [19,42] and prevent the occurrence of damage of the skeletal muscles resulting from OP compound-induced

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AChE inhibition [38].

It was ascertained that memantine owes its beneficial effect against Alzheimer disease via its neuroprotective antiglutamatergic effect [43] and the same mechanism is proposed to be behind its antidotal activity against OP compounds [44,45]. In some experiments *in vivo*, however, memantine also demonstrated protection of AChE in brain and diaphragm from inhibition caused by soman [19], suggesting that this mechanism might also contribute to its antidotal properties.

For this reason, the aim of this study was to investigate the interactions of memantine and its metabolite (1-amino-3-hydroxymethyl-5-methyl adamantine, Mrz 2/373) with AChE *in vitro* as well as their effect on kinetics of the soman-induced AChE inhibition, aging and asoxime (HI-6 dichloride, 4-Carbamoyl-1-[({2-[(E)-(hydroxyimino) methyl]-1-pyridiniumyl}methoxy)methyl]pyridinium dichloride)-induced reactivation. Their structural formulae are presented in Fig. 1.

2. Materials and methods

2.1. Materials

Bovine erythrocyte AChE (EC 3.1.1.7, type XIII, 0.25–1.0 unit/mg solid) was purchased from Sigma, Munich, Germany. Memantine and Mrz 2/373 were a gift from Merz + Co, GmbH & Co., Frankfurt/M, Germany. Barbital buffer (pH 8.6) was purchased from Merck, Germany. Soman and HI-6 were obtained from Military Technical Institute, Belgrade, Serbia.

2.2. Methods

AChE activity was determined according to the method of Ellman et al. [46].

The study consisted of three parts: (1) investigation of interaction of memantine or Mrz 2/373 with AChE *in vitro*, (2) the effect of memantine or Mrz 2/373 on soman-induced AChE inhibition and (3) their potential influence on aging of the soman-inhibited AChE.

1) In the first part of the *in vitro* experiments AChE and adamantanes were incubated at pH 7.3 and 37 °C. The effects of memantine and Mrz 2/373 (1 mmol/l each) on AChE activity were obtained and used for the construction of the Lineweaver-Burke plot and thereafter the types of inhibition were analysed and the kinetic constants of inhibition were calculated according to Hallek and Szinicz [47] and Bisswanger et al. [48]. The inhibition constants were calculated as follows:

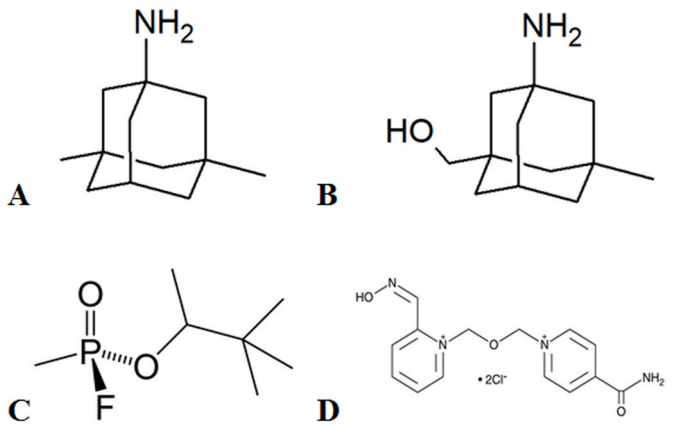

Fig. 1. Structural formulae of A) memantine (1-amino-3,5-dimethyladamantane, Mrz 2/145), B) Mrz 2/373 (1-amino-3-hydroxymethyl-5-methyl adamantine), C) soman (1,2,2-trimethylpropylmethylphosphonofluoridate) and D) asoxime (HI-6 dichloride, 4-carbamoyl-1-[({2-[(E)-(hydroxyimino)methyl]-1-pyridiniumyl}methoxy)methyl]pyridinium dichloride).

$K_{ii} = I/(y \cdot V_{max} - 1)$; $K_i = -K_m \cdot I/[1 + (I/K_{ii}) + Km \cdot x]$,

where K_{ii} and K_i are dissociation constants of the complex enzyme-substrate-inhibitor (constant of non-competitive inhibition, i.e. inhibition at the allosteric site and constant of competitive inhibition, i.e. inhibition at the active centre, respectively), x and y are intersections of the graph with abscise and ordinate, respectively, V_{max} is the maximum reaction rate, K_m is Michaelis-Menten constant and I is concentration of the inhibitor. From the graphs for the competitive and non-competitive type of inhibition the slope was calculated according to the formula slope $= K_m/V_{max}$ $(1 + I/K_i)$, where K_m is Michaelis-Menten constant, V_{max} is the maximum reaction rate, I is concentration of the inhibitor and K_i is a dissociation constant of the enzyme-inhibitor complex (constant of competitive inhibition, i.e. inhibition at the active centre of the enzyme).

Calculations of values needed for construction of the enzyme kinetics graphs were performed by using the SPSS version 18.0 program and the enzyme kinetics was shown by using the linear regression analysis.

In a separate set of the experiment, under the same conditions described above, the substrate concentration was fixed at 0.05 mmol/l and adamantane-induced AChE inhibition was ascertained at concentrations of memantine 1 and 3 mmol/l or Mrz 2/373 1 mmol/l.

2) Different concentrations of memantine (0.1, 0.5 and 1 mmol/l) and its metabolite Mrz 2/373 (0.1, 0.5 and 1 mmol/l) were incubated with AChE (1 mg in 4 ml of barbital buffer, pH 7.3 at 37 °C). Inhibition of AChE started with soman (final concentration of 7.5 nmol/l). After 5, 10, 15 and 20 min, samples of AChE were taken, and its activity was assayed according to Ellman et al. [46]. Based on the slope of the curve in a graph log remaining AChE activity-time, the half-time ($t_{1/2}$) of inhibition was calculated in the absence and in the presence of the two adamantanes. The phosphonylation constant was calculated according to the formula $t_{1/2} = 0.693/K_i$, where K_i is the phosphonylation constant and $t_{1/2}$ is the inhibition half-time.
3) The third part of the study comprising inhibition, aging, reactivation in the presence of the bispyridinium oxime asoxime (HI-6, 4-Carbamoyl-1-[({2-[(E)-(hydroxyimino)methyl]-1-pyridiniumyl}methoxy) methyl]pyridinium dichloride) and assay *in vitro* was performed essentially as described by Hallek and Szinicz [47]. Briefly, there were four phases of this experiment: (a) inhibition by soman 5×10^{-8} mol/l for 30 min at pH 10 and at 0 °C (these extreme conditions were set in order to prevent aging of the soman-AChE complex), (b) aging – incubation for 5 min with adamantanes at pH 7.3 and at 37 °C, (c) reactivation - incubation with HI-6320 μmol/l for 20 min at pH 7.3 and at 37 °C and (d) AChE assay according to Ellman et al. [46].

3. Results

3.1. Effect of adamantanes on the activity of bovine erythrocyte AChE in vitro

Memantine or Mrz 2/373, incubated at concentrations of 1 mmol/l, showed the inhibitory potential for AChE. It can be seen from the graph where increasing concentrations of the substrate acetylthiocholine iodide (ASChI) were plotted against the difference in extinction after 30 s and where both the memantine and the Mrz 2/373 lines were above the control one, registered without presence of either of the two adamantanes. The control graph and the graph of memantine concentration of 1 mmol/l intersects to the left of the y axis, suggesting the mixed type of enzyme inhibition, partly at the active centre and partly at the adjacent allosteric site. At the same time, the graph of its metabolite Mrz 2/373 intersects with the control one at the y axis, suggesting the pure competitive inhibition at the acetylcholine-binding site (Fig. 2).

AChE and adamantanes were incubated at pH 7.3 and 37 °C and

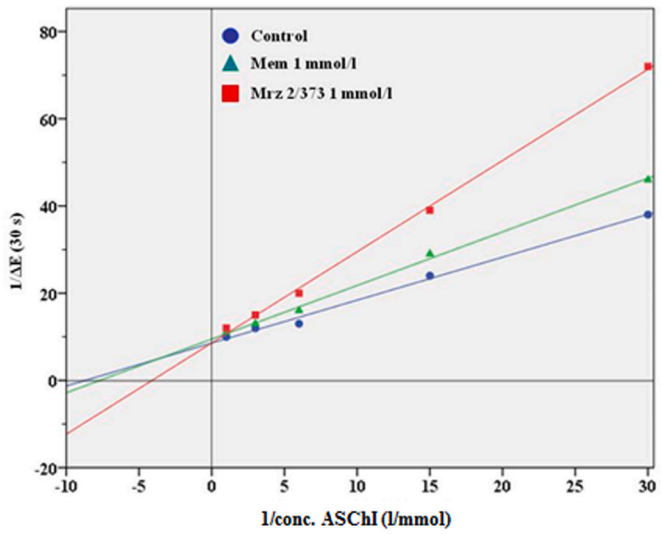

Fig. 2. Effects of memantine and its metabolite Mrz 2/373 on the activity of bovine erythrocyte AChE *in vitro* (Lineweaver-Burke's transformation).

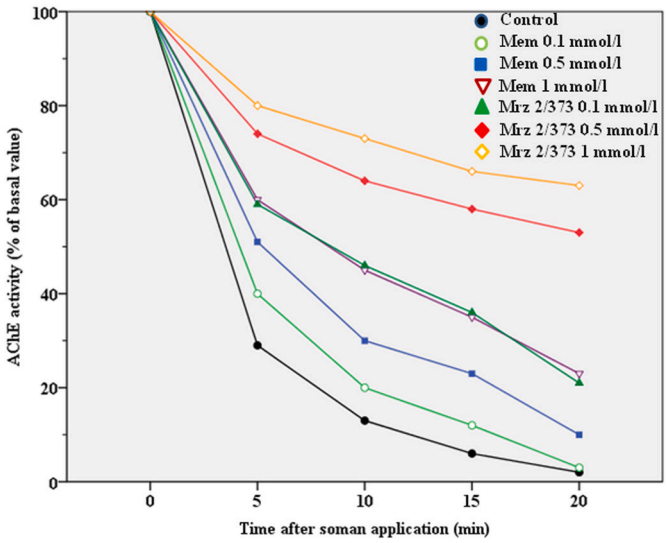

Fig. 3. Effects of memantine and its metabolite Mrz 2/373 on the rate of inhibition of bovine erythrocyte AChE by soman *in vitro*. Final soman concentration was 7.5 nmol/l. AChE, soman and adamantanes were incubated at pH 7.3 and 37 °C and enzyme activity determined spectrophotometrically according to Ellman et al. [46].

enzyme activity determined spectrophotometrically according to Ellman et al. [46]. 1/ΔE (30 s) = difference in extinction after 30 s. ASChI stands for acetylthiocholine iodide.

The inhibition constants of the two adamantanes are shown in Table 1. Their concentrations were 1 and 3 mmol/l for memantine and 1 mmol/l for Mrz 2/373.

Inhibition constants for memantine were K_i = 755 μmol/l and K_{ii} = 4528 μmol/l, with the ratio K_{ii}/K_i = 6.0, suggesting that memantine is a 6 times more potent inhibitor of the binding site for ACh than for the allosteric site (Table 1). Mrz 2/373 was a more potent inhibitor of AChE than memantine, with K_i = 504 μmol/l. To illustrate this, in a separate experiment (not shown), at substrate concentration of 0.05 mmol/l, memantine 1 mmol/l and the same concentration of Mrz 2/373 assured 16% and 41% inhibition; the concentration of memantine had to be increased to 3 mmol/l to result in a similar level of inhibition of AChE (46%).

3.2. *Effect of adamantanes on the kinetics of soman-induced inhibition of bovine erythrocyte AChE in vitro*

From Fig. 3 it appears that adamantanes decrease the rate or even prevent the effects of soman in a concentration-dependent manner, with Mrz 2/373 1 mmol/l producing the most potent effect.

For example, similar levels of the remaining AChE activity were achieved 5 min after adding soman alone into the medium (27.5%) and 20 min after addition of soman and memantine 1 mmol/l in the medium (27.2%). Very similar results to memantine 1 mmol/l were obtained with Mrz 2/373 0.1 mmol/l. Its concentrations of 0.5 and 1 mmol/l were more effective in such a way that even after 20 min after addition of soman and Mrz 2/373 1 mmol/l into the medium the remaining AChE activity was just below 60% of the initial value.

Table 1
Constants and types of inhibition of the bovine erythrocyte AChE for memantine and its metabolite Mrz 2/373.

Inhibitor	K_i (μmol/l)	K_{ii} (μmol/l)	Type of inhibition
Memantine	755	4528	Mixed
Mrz 2/373	504	–	Competitive

K_i = inhibition constant at acetylcholine-binding site of bovine erythrocyte AChE, K_{ii} = inhibition constant at allosteric site of AChE. AChE and adamantanes were incubated at pH 7.3 and 37 °C and enzyme activity determined spectrophotometrically according to Ellman et al. [46].

Quantitative aspects of this adamantane effect on the rate of soman-induced AChE inhibition are shown in Table 2.

Data in Table 2 show that memantine and Mrz 2/373 decrease the rate of soman-induced phosphonylation of AChE in a concentration-dependent manner, with Mrz 2/373 at concentration of 1.0 mmol/l being the most potent one, since it delayed the enzyme inhibition by a factor of 9.33.

3.3. *Effects of memantine and Mrz 2/373 on aging and HI-6-induced reactivation of AChE inhibited with soman in vitro*

Table 3 presents data on remaining AChE activities for two concentrations of memantine (1 and 10 mmol/l) and one concentration of Mrz 2/373 (1 mmol/l) after the phases of inhibition, aging and reactivation.

Results presented in Table 3 show that the presence of either of the two adamantanes, and particularly memantine 10 mmol/l, provided much better reactivation of AChE activity, in comparison with the controls without the adamantanes.

4. Discussion

Experimental data *in vivo* did not demonstrate that therapeutic doses

Table 2
Effects of memantine and its metabolite Mrz 2/373 on the rate of soman-induced inhibition of bovine erythrocyte AChE *in vitro*.

Adamantane (mmol/l)	K_i (μmol/l)	$t_{1/2}$ (min)	Adamantane protective factor[a]
None	0.2566	2.70	–
Memantine (0.1)	0.1909	3.63	1.34
Memantine (0.5)	0.1193	5.81	2.15
Memantine (1.0)	0.0895	7.74	2.87
Mrz 2/373 (0.1)	0.0900	7.70	2.85
Mrz 2/373 (0.5)	0.0365	19.01	7.03
Mrz 2/373 (1.0)	0.0274	25.20	9.33

[a] Adamantane protective factor is a ratio of $t_{1/2}$ (min) of the memantine or Mrz 2/373 concentration in question and $t_{1/2}$ (min) of control without any adamantane. Final soman concentration was 7.5 nmol/l. AChE and adamantanes were incubated at pH 7.3 and 37 °C and enzyme activity determined spectrophotometrically according to Ellman et al. [46].

Table 3
Effect of memantine and Mrz 2/373 on AChE after inhibition with soman, aging and reactivation by HI-6 *in vitro*.

Effector (concentration)	AChE activity after reactivation (% of the initial activity)	Additional AChE reactivation vs. control[a] (%)
None (control)[a]	8.1	0
Memantine (1 mmol/l)	30.6	+22.5
Memantine (10 mmol/l)	41.9	+33.9
Mrz 2/373 (1 mmol/l)	16.1	+8.0

[a] Control = AChE + soman + HI-6. In all experiments there were four consecutive phases of this experiment: (1) inhibition by soman 5×10^{-8} mol/l for 30 min at pH 10 and at 0 °C to prevent aging of the soman-AChE complex, (2) aging – incubation for 5 min with adamantanes at pH 7.3 and at 37 °C, (3) reactivation - incubation with HI-6320 μmol/l for 20 min at pH 7.3 and at 37 °C and (4) AChE assay according to Ellman et al. [46].

(18 mg/kg *sc*) of memantine have the potential to inhibit AChE [15,19,39]. In the present *in vitro* study, however, both memantine and its metabolite Mrz 2/373 acted as AChE inhibitors – memantine as a mixed one and Mrz 2/373 as a pure competitive one. The concentrations used were in the millimolar range. In another experimental study in rats memantine, administered at a dose of 2.5 mg/kg *ip*, produced plasma concentrations within a range of 10–245.6 μmol/l [49]. It should be also taken into consideration that positive antidotal effects against soman poisoning in the same species were obtained when the doses were much higher - 18–72 mg/kg *sc* [19]. It is reasonable to assume that the corresponding plasma concentrations would be in the millimolar range, which makes the present results obtained *in vitro* extrapolable to the *in vivo* situation.

At the same time, it was shown that memantine decreased the level of AChE inhibition induced by various AChE inhibitors, including soman *in vivo* [15,19,38]. As showed earlier [19], antidotal doses of memantine of 18–72 mg/kg *sc* are relatively high and they result in tissue concentrations of memantine and its metabolite Mrz 2/373 that are close to their K_i and K_{ii} values obtained in the present study *in vitro*. It appears that effective blood concentrations close to the ones used in the present *in vitro* experiment can be achieved after administration to rats *in vivo* [50]. Since memantine did not influence the binding of ambenonium and decamethonium to the active site of the rat brain AChE, respectively [15], it can be assumed that memantine binds to another position close to the AChE active site in such a manner that it changes the conformation of the enzyme, rendering it more resistant to binding of the inhibitor. The present *in vitro* results support these findings, since memantine or Mrz 2/373, both at concentration of 1 mmol/l, decreased the rate of soman-induced AChE inhibition by 2.87- and 9.33-fold, respectively. For this reason it is logical to assume that the protection of AChE from inhibition, either by memantine or Mrz 2/373, represents an important mechanism of the memantine's antidotal activity against OP compounds including soman [19,40].

The hypothesis that memantine can reactivate the already inhibited AChE should be discarded for both theoretical and empiric reasons. Namely, memantine lacks the oxime functional group and therefore cannot induce a nucleophilic attack on the phosphorus atom of the active centre of the AChE. In addition, memantine 2×10^{-5} mol/l did not reactivate AChE inhibited with tabun, sarin, soman or VX [51].

Although both Mrz 2/373 and especially memantine provided significantly higher AChE activities versus control in the experimental *in vitro* model of soman-induced inhibition, aging and reactivation, it is too preliminary to deduce that the adamantanes directly decrease the rate of aging of the soman-AChE complex. In addition to it, there are no reports in the literature to support such an antidotal mechanism. At the same time, in the present experiment adamantanes delayed/protected from inhibition by soman the AChE *in vitro*. As a consequence, via this mechanism, the adamantanes might decrease the part of AChE available for interaction with soman and further dealkylation and aging. This assumption is, however, not supported by the lack of parallelism between the effects of memantine and Mrz 2/373 against soman inhibition on one side and their affinity to decrease the results of aging of the AChE-soman complex; Mrz 2/373 was more potent in the former and memantine in the latter experimental model.

5. Conclusion

It could be concluded that memantine and Mrz 2/373 can prevent AChE from inhibition by soman, which could, along with known memantine's neuroprotective activity, explain its potent antidotal effect in soman poisoning. The potential effect on aging of the soman-AChE complex warrants further studies.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cbi.2021.109463.

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