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Studies on the role of central catecholaminergic mechanisms in the antidotal effect of the oxime HI 6 in soman poisoned mice

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Abstract. The effects of atropine and the oxime HI 6 on running performance, brain and plasma cholinesterase activity and brain catecholamines were investigated in mice intoxicated with sublethal doses of soman (100 μg/kg s.c.). The running time on a rotating mash wire drum (total running time 60 min) after injection of soman was reduced to 17.2 min. Treatment with atropine (10 mg/kg i.p.) or HI 6 (55 mg/kg i.p.) improved the running peformance to 48.2 and 44.8 min, respectively. Cholinesterase activity was decreased in soman poisoned mice to 47.3% in plasma and 43.5% in brain. Therapy with the oxime HI 6 resulted in a reactivation of soman-inhibited peripheral cholinesterase to 76.6%, but failed to reactivate central cholinesterase. Dopamine levels in mice brain were elevated in soman poisoning by 23.2%, whereas noradrenaline levels remained unchanged. The increase in brain dopamine levels was antagonized by atropine as well as by HI 6. The results of this study lead to the speculation that central dopaminergic mechanisms may be involved in soman toxicity as well as in the antidotal action of atropine and the mainly peripherally acting oxime HI 6.

Key words: Cholinesterase – Soman – Oxime – HI 6 – Dopamine

Introduction

The combination of atropine, an oxime and diazepam is an effective therapy in poisoning with cholinesterase (ChE) inhibiting organophosphates. However, soman (1,2,2-trimethylpropymethylphosphonofluridate), an extremely potent anticholinesterase agent, is resistant to this treatment. Recently, a series of new bispyridinium oximes originating from the laboratory of Prof I Hagedorn at Freiburg (FRG) have been shown in several animal species to be very effective against soman poisoning. Among them, HI 6 was the least toxic and most effective one (Clement 1981; Wolthuis et al. 1984; Arbogast 1987).

The beneficial effects of HI 6 are generally thought to be due to the reactivation of soman-inhibited acetylcholinesterase (AChE), but the mechanism of action of the oxime is not fully elucidated: Soman exerts its effects predominately on the central nervous system, whereas HI 6 crosses the blood-brain barrier only in small amounts and reactivates peripheral but only causes a slight reactivation of central acetylcholinesterase. Therefore peripheral reactivation of soman inhibited acetylcholinesterase (Clement 1982; Clement and Lockwood 1982), direct anticholinergic actions (French et al. 1983) and other noncholinergic central mechanisms (Lundy and Shih 1983) have been assumed to explain the mechanism of the protective action of HI 6 in soman poisoning. Certain central actions of anticholinesterases seem to be exerted via a release of catecholamines (Varagic and Krstic 1966; Van Meter and Karczmar 1971; Glisson et al. 1974). In organophosphate intoxication an elevation in dopamine levels and a decrease in noradrenaline levels have been shown in various brain parts (Glisson et al. 1972, 1974; Coudray-Loucas et al. 1982). The purpose of this study was to determine if central catecholaminergic mechanisms may be involved in the protective effect of HI 6 in organophosphate poisoning. Therefore we studied the effects of the antidotes atropine and HI 6, alone or in combination, on motor performance, central and peripheral cholinesterase activity and central catecholamine levels in soman poisoned mice.

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Materials and methods

White male NMRI mice (Lippische Versuchstierzucht, Extertal-Bösingfeld, FRG), weighing 20–25 g with tap water and standard mice chow ad lib (Altromin) were used. Soman was 92% pure (titrimetrically). HI 6 (pyridinium-1-(((4-carbamoyl pyridinio)methoxy)methyl)-2-(hydroxyiminomethyl)dichloride) was a gift from Dr Clement, Suffield, Canada. Atropine sulfate was obtained from Merck, Darmstadt, FRG, noradrenaline hydrochloride, dopamine hydrochloride and 3,4-dihydroxybenzylamine hydrobromide were obtained from Sigma, Munich, FRG. All other chemicals were of analytical purity and were purchased from Sigma, Munich or Merck, Darmstadt (FRG).

The animals were allowed to adapt for 10 days and were then trained for 3 consecutive days, once daily, for 60 min.

Running performance. To test the effect of atropine and HI 6 on running performance of soman poisoned mice a rotating (14 rpm) mash wire drum, 20 cm in diameter, was used. The mice received soman and the antidotes immediately before the running period of 60 min. The time until the animals fell from the drum and the number of animals which performed the full running period of 60 min were

registered. Before injection and after the performance experiment a modified neurologic screening program was performed, according to the schedule first published by Irwin (1968) testing 26 parameters. The dose of soman administered (100 µg/kg) was the model specific ED_{95} corresponding to about 50% of the LD_{50} (Oldiges and Schoene 1970). To test the efficacy of the antidotes a model specific ED_5 was used for atropine (10 mg/kg) and HI 6 (55 mg/kg), respectively. The animals, attributed at random, received soman s.c. and subsequently atropine and/or HI 6 i.p. by a double blind procedure. Four hours after the injection of soman and antidotes the animals were anesthetized with ether and sacrificed by exsanguination. The brains were removed immediately thereafter and processed either for the measurements of cholinesterase activity or catecholamine levels or microscopical examination.

Determination of cholinesterase activity. Plasma cholinesterase activity was measured photometrically according to Ellman et al. (1961). For measurement of brain cholinesterase activity mouse brains (about 400 mg wet weight) were homogenized in 1.5 ml ice-cold 0.9% NaCl and cholinesterase activity was measured according to Ellmann et al. (1961) as well as titrimetrically according to Nenner (1970).

Measurement of catecholamine levels in mice brain. Brains were homogenized in 1.5 ml ice-cold $HClO_4$. Following centrifugation (4000 *g*, 15 min, 4° C) the supernatants were purified on Sephadex G 10 columns as described by Westerink (1983). Recoveries were 54.6 ± 16.4% for dopamine and 44.3 ± 15.5% for noradrenaline (mean ± SD, $n = 4$). Catecholamine standards were weekly prepared in 0.1 M $HClO_4$. Dihydroxybenzylamine hydrobromide was used as internal standard. A Hewlett Packard (Munich, FRG) liquid chromatograph 1084 B equipped with a cation exchange column (Nucleosil 100- 5 SA, 8 × 4 × 200 mm; Macherey-Nagel, Düren, FRG) and a Metrohm (Herisau, Switzerland) electrochemical detector (model E 656 with 641 VA detector) equipped with a glassy carbon electrode were used. The electrode potential was set at 0.65 V against a Ag/AgCl/c(KCl)-reference electrode (range 5 nA). Samples (100 µl) were injected with a variable injector kit (Hewlett Packard 79841 A). The mobile phase consisted of an acetate-citrate buffer (5.75 g/l citric acid, 9.08 g/l sodium acetate 3 H_2O, 1.73 g/l NaOH and 50 mg/l EDTA, pH 5.2) and 10% methanol. The solutions were filtered (0.5 µm Millipore filter; Eschborn, FRG) and degassed.

Statistics. The results were checked for significant differences by one-way Student's *t*-test on a $p \leq 0.05$ level.

Results

Effects of atropine and HI 6 on running performance

In animals receiving soman alone all parameters of the behavioural screening program were significantly worsened. The running performance and number of animals able to run the full time period (60 min) subsequent to the injection of soman proved to be the most sensitive parameters for the evaluation of the effects of atropine and HI 6 (Fig. 1), and therefore other data are not shown in the text. Soman (100 µg/kg s.c.) alone diminished the running time from 59.4 min to 17.2 min; the number of animals which performed the full running period decreased from 97.5% to 12%. Atropine (10 mg/kg i.p.) or HI 6 (55 mg/kg i.p.) caused a significant prolongation of the running time to

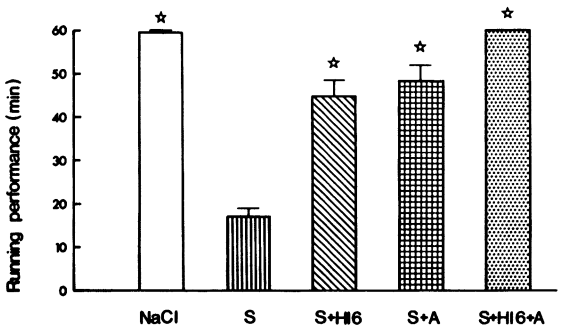

Fig. 1. Effect of atropine and HI 6 on motor performance of mice impaired by soman. The running period of mice immediately after treatment with 0.9% NaCl s.c./i.p. ($n = 40$), soman (100 µg/kg) s.c./0.9% NaCl i.p. ($n = 50$), soman (100 µg/kg) s.c./HI 6 (55 mg/kg) i.p. ($n = 30$), soman (100 µg/kg) s.c./atropine (10 mg/kg) i.p. ($n = 30$) and soman (100 µg/kg) s.c./HI 6 (55 mg/kg) i.p./atropine (10 mg/kg) i.p. ($n = 30$) was measured on a rotating (14 rpm) mash wire drum (20 cm in diameter). Mean running time ± SEM is shown. * significant difference to the soman group, $p \leq 0.05$

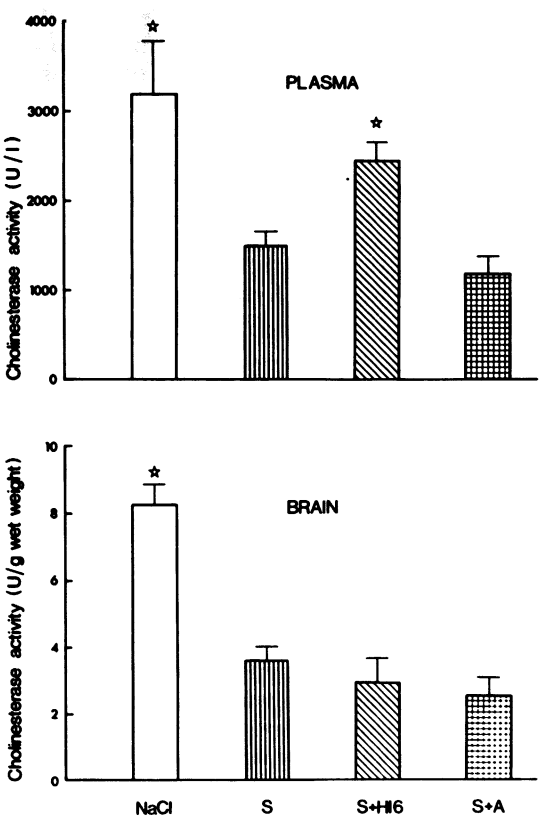

Fig. 2. (a) Cholinesterase activity in mice plasma after the injection of 0.9% NaCl ($n = 3$), soman ($n = 7$), soman + HI 6 ($n = 6$) and soman + atropine ($n = 6$). Mean ± SEM. **(b)** Cholinesterase activity in mice brain after the injection of 0.9% NaCl ($n = 3$), soman ($n = 3$), soman + HI 6 ($n = 4$) and soman + atropine ($n = 5$). Mean ± SD. * significant difference to the soman group, $p \leq 0.05$

48.2 and 44.8 min, respectively and increased the number of mice which performed the full running period to 62.7% and 72.6%, respectively. Moreover, in the group treated with atropine plus HI 6 all animals were able to run the full experimental period of 60 min (Fig. 1).

Effects of atropine and HI 6 on ChE activity

Effects of atropine and HI 6 on cholinesterase activity were measured in plasma (Fig. 2a) and homogenates of the whole brain (Fig. 2b) 4 h after the injection of soman and the antidotes. After soman alone plasma cholinesterase activity was reduced from 3,188 U/l (NaCl s.c. group) to 1507 U/l (47.3%). HI 6 i.p. led to a significant reactivation of plasma cholinesterase activity to 2442 U/l (76.6%) (Fig. 2a).

In brain homogenates cholinesterase activity of soman poisoned animals was decreased from 8.23 U/g (NaCl s.c. group) to 3.58 U/g (43.5%). In contrast to the effects of HI 6 on cholinesterase activity in plasma, HI 6 treatment did not reactivate soman-inhibited brain cholinesterase activity (2.9 U/g) (Fig. 2b). Similar results were obtained by titrimetric determination of cholinesterase activities in brain homogenates (NaCl s.c.: 10.4 U/g; Soman s.c.: 3.7 U/g; Soman s.c. + HI 6 i.p.: 2.9 U/g). In soman poisoned mice treated with atropine i.p. a slight decrease in cholinesterase activities relative to the soman group was measured in the plasma as well as in the brain homogenates, but the differences were not statistically significant.

Effects of atropine and HI 6 on catecholamine levels in mice brain

As previously shown in rats in our laboratory (Katzlmeier, unpublished work), an increase in brain dopamine level (+23.3%, $p \leq 0.05$) was also found in mice poisoned with soman (Fig. 3b). The increase in the dopamine level in soman poisoning was fully antagonized by atropine as well as by the combination of atropine plus HI 6. It was shown in these experiments for the first time that not only atropine but also HI 6 alone almost completely prevented the increase in brain dopamine levels caused by soman (Fig. 3b). In contrast to the results of other authors (Glisson et al. 1974; Coudray-Loucas et al. 1983) the brain noradrenaline levels were found not to be significantly different from control animals in mice receiving soman without further treatment and in mice treated with the antidotal compounds (Fig. 3a).

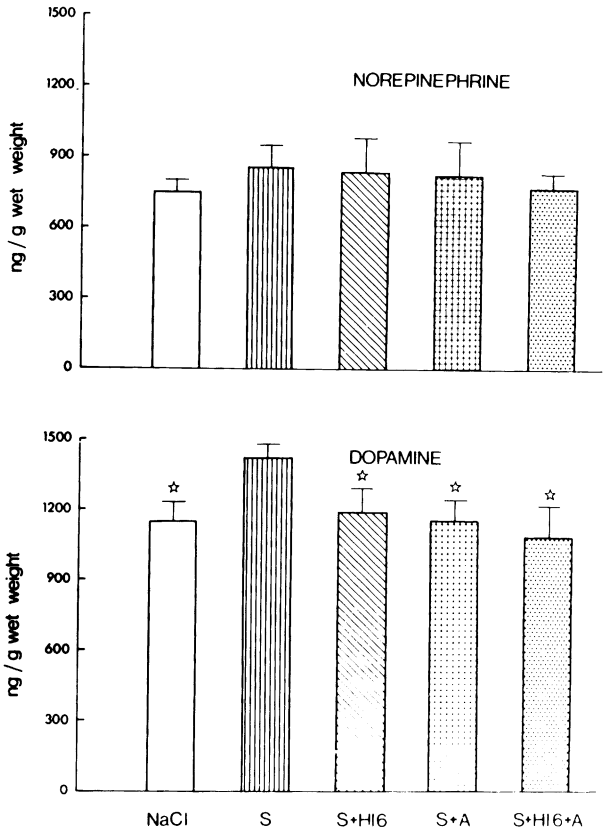

Fig. 3. Dopamine and noradrenaline levels in mice brain after the injection of 0.9% NaCl (n = 7), soman (n = 7–8), soman + HI 6 (n = 7), soman + atropine (n = 10), and soman + HI 6 + atropine (n = 5). Mean ± SEM. * significant difference to the soman group, $p \leq 0.05$

Discussion

The results presented show a decrease in motor performance (Fig. 1) accompanied by a central and peripheral AChE inhibition (Fig. 2) and an increase in brain dopamine content (Fig. 3) in mice receiving a non-lethal dose of soman. The motor performance improved in mice when treated either with atropine or HI 6 or both (Fig. 1). Because of the drastic improvement in running performance due to atropine, the impact of soman on motor performance seems to be mediated also by other mechanisms than by the impairment of neuromuscular transmission. Although atropine is primarily an antimuscarinic drug and HI 6 a peripheral reactivator of cholinesterase, the improvement in both cases was accompanied by a normalisation of the dopamine content in the brain. As the central dopamine content is important for the function and control of skeletal muscles, one might speculate that the disturbance and the improvement of motor performance is mediated by the respective changes in central dopamine content.

An increase in brain (striatum) dopamine content in rats treated with soman was shown by Coudray-Loucas et al. (1983) together with a decrease in noradrenaline content in the hypothalamus. Preliminary data from our laboratory also indicate a mainly striatal increase in dopamine content, as soman led to a higher increase in the striatum (+50%) compared to total brain homogenate (+23%) (not shown). A similar effect, namely an increase in dopamine and decrease in noradrenaline content due to diisopropylfluorophosphate (DFP) in rabbits, was reported by Glisson et al. (1972, 1974). Effects of anticholinesterase on central catecholaminergic systems were also shown by Varagic and Krstic (1966), Van Meter and Karczmar (1971) and by Anden and Wachtel (1977). These central catecholaminergic actions were explained by cholinergic interactions with catecholaminergic pathways via the stimulation of muscarinic receptors (Van Meter and Karczmar 1971; Anden and Wachtel 1977; Morgan and Pfeil 1978). Atropine was reported by Glisson et al. (1972, 1974) to prevent the dopamine increase in rabbits due to DFP. The results presented show that HI 6, a quaternary ammonium compound, only very small amounts of which penetrate into the brain (Klimmek et al. 1986), also decreases the

cerebral dopamine content in soman poisoning (Fig. 3b). In agreement with these results, no reactivation of cerebral ChE by HI 6 was found in the experiments presented, although in the serum a marked effect was observed (Fig. 2). In contrast to the data presented and those of Klimmek and Eyer (1986), Clement (1982) reported some central reactivation by HI 6 in rats after low doses of soman but using higher doses of HI 6 (125 mg/kg). Antimuscarinic (Clement 1981) and ganglionic blocking properties (Lundy and Tremblay 1979) were also reported for HI 6. As high doses of the oxime are necessary for these effects, other central effects than reactivation seem to be even less probable.

Nevertheless, a decrease in the central dopamine level in organophosphate poisoning seems to be possible also by some peripherally mediated mechanisms as shown by Glisson et al. (1972 and 1974). These authors reported that the non-centrally acting atropinemethylnitrate was even more effective than atropine in decreasing brain (striatum) dopamine content increased by DFP. Although a different compound with regard to the primary mechanism, HI 6 acts also primarily on the peripheral cholinergic nervous system. These data support the assumption that the soman-induced increase in central dopamine level can be improved by a peripheral effect of HI 6 (reactivation), which is associated with an improvement of motor performance.

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