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TREATMENT OF BEHAVIORAL IMPAIRMENT CAUSED BY SOMAN IN MICE

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Disturbed function of various organs may be caused by compounds influencing cholinergic synaptic transmission. Besides of lethal effects disturbances of memory or physical performance, caused by sublethal doses of highly toxic cholinesterase (ChE) inhibitors, might also represent a major problem.

The purpose of this study was to investigate the sublethal effects of soman on memory and physical performance in mice and to assess the response of these disturbances to the treatment with atropine and the reactivator HI 6.

Materials and Methods

White male NMRI mice (Lippische Versuchstierzucht, Extertal-Bösingfeld, FRG), weighing 20-25g, with standard mice chow (Altromin) and tap water ad lib were used. The animals were allowed to adapt for 10 days and were then trained once daily for 6 weeks in a radial maze for spatial memory experiments or 3 days on a rotating mash wire drum for physical performance assessment. Groups of ten randomly attributed animals were used.

Radial maze experiments: A 16 arm radial maze was used modified accor-ding to Halas et al. (1983) from Olton et al. (1976, 1977). 8 arms were supplied alternatively with food pallets. The repeated entering of an arm (working memory error) and entering of a non supplied arm (reference memory error) (Olton et al 1980) were registered.

Physical performance: The mice were allowed to run on a rotating (14 rpm) mash wire drum (20 cm diam.). Mean running time and the number of animals unable to run the full running period (60 min) were registered.

Assessment of the behavioral and physiologic state of the animals: Before the treatment and the exercise (radial maze/-mash wire drum) and after that a comprehensive observational assessment of the behavioral and physiologic state of each animal according to Irwin (1968) was performed. The difference of the value (arbitrary units) before and after the experiment was used. The parameters measured are listed in Fig 1.
Cholinesterase (ChE) activity: The activity was measured in plasma, erythrocytes and in brain homogenates, removed after the experiment from animals anesthetized with ether, according to Ellman et al. (1961).
Statistics: The results were checked for significant differences by the analysis of variance, Scheffe test (a=0,05).

Results and Discussion

The spatial memory (working and reference memory error) in the radial maze was not markedly changed by soman, 0-80 ug/kg s.c. The working memory error is shown in fig. 1.

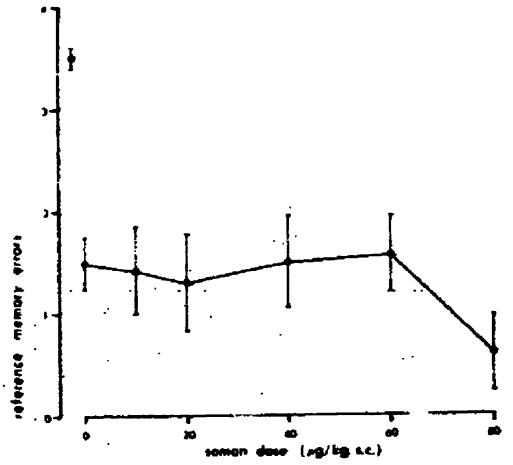

Fig. 1: Effect of soman on spatial memory in mice.
White male NMRI mice were placed on the central platform of a 16 arm radial maze, with food pallets on the end of 8 of them. Correct (supplied arms) and incorrect (non supplied arms = reference memory error and supplied arms repeatedly = working memory error) enterings were registered.

Contrary to the spatial memory a dose dependent decrease of motor performance, i.e. mean running time and number of animals unable to run the full experimental period, was observed in mice receiving soman, 0 - 100 ug/kg s.c. (fig. 2), with a sharp decrease at about 50 ug/kg.
Lethality was observed after doses of soman higher than 100 ug/kg s.c.(fig. 2).

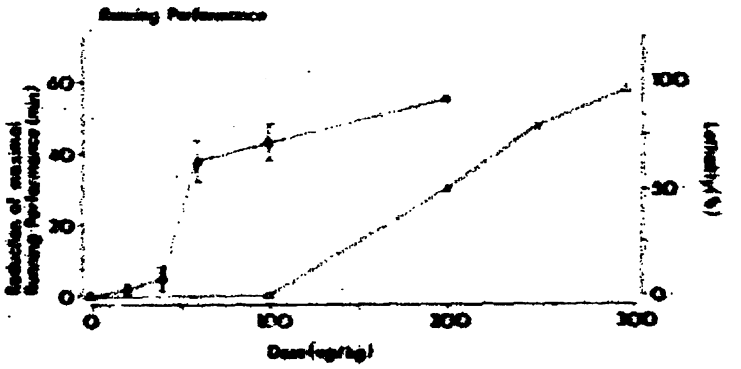

Fig. 2: Effect of soman on running time and survival of mice. Running time was measured on a rotating mash wire drum(see methods) in animals treated with various doses of soman s.c. before the exercise. Mean running time ± SEM is shown (n = 10).

In addition to the sharp decrease of motor performance at about 50 ug/kg s.c. a similar decrease in sensoro motor responses, tail pinch, toe pinch, corneal, pinna (fig. 3) and startle response, was observed as well as a decrease in limb and body tone.
In order to assess the therapeutic effect of the antidotes the ED_{95} of soman for the decrease in running time was calculated (0.1 mg/kg) and injected s.c. For treatment the corresponding ED_5 of HI 6 (55 mg/kg) and the most effective dose of atropine for the improvement of running time (10 mg/kg), were given i.p., immediately after soman.
In addition to the running performance a variety of behavioral, physiologic and neurologic parameters were changed by

soman treatment. The effects and the impact of therapy with atropine and/or HI 6 are summarised in table 1.

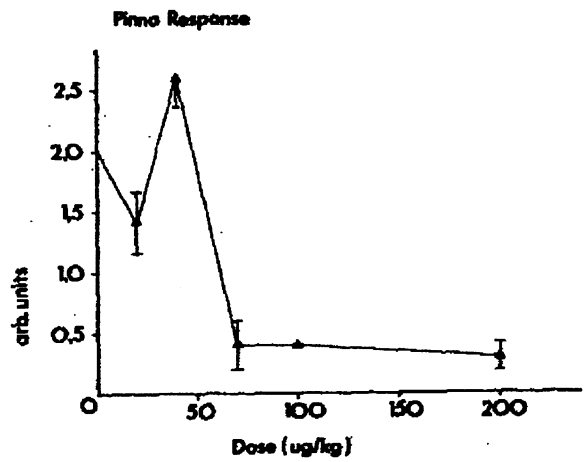

Fig. 3: Effect of soman on the pinna response in mice. Difference of the value before and after treatment in arbitrary units is shown (mean ± SEM; n = 10).

Table 1: Effect of HI 6 and atropine on various parameters of mice treated with soman.

	NaCl	Soman	Soman HI 6	Soman Atrop.	Soman Atrop HI 6
I. Running Performance					
-Running Time (min)	59*	17	52*	39*	60*
-Failure Rate (%)	5	90	20	50	0
II. Behavioral					
A. Spontaneous Activity					
- Body Position	1.6*	0	1.1	2.1*	1.8*
- Locomotor Activity	1.8*	0.8	1.1	2.1*	1.8*
- Bizarre Behaviour	2.1	3.6	2.5	2.0	2.1
B. [illegible] Affective Responses					

- Transfer Arousal	2.1	1.4	1.4	1.8*	1.8*
- Provoked Biting	2.0	1.8	1.8	1.9	1.6*
- Positional Struggle	1.6	0	1.1	2.1	1.8
C. Sensoro-Motor Responses					
- Visual Placing	2.1*	1.5	2.0*	1.5*	1.9*
- Tail Pinch	1.8*	0.2	1.4	2.0*	1.6*
- Toe Pinch	2.0*	0.5	1.5	1.8*	1.8
- Corneal	2.0*	0.9	2.0*	2.0*	1.9*
- Pinna	1.8	0	1.3	1.9	1.7
- Startle	2.1	1.5	1.7	2.5	1.8
III.Neurologic					
A. Muscle Tone					
- Body Tone	1.9*	1.0	2.0*	1.2	1.5*
- Abdominal Tone	2.2*	2.7	1.9	1.9	1.8*
- Limb Tone	2.2	1.1	1.8	1.6	1.7
- Grip Strength	2.1	1.1	2.0	2.2	2.2
B. CNS-Excitation					
- Tremor	2.3*	3.6	2.9	2.6*	2.2*
- Convulsions	2.0	3.8	2.2	2.0	2.0
IV. Autonomic					
A. Eyes					
- Pupil Size	2,0	1.0	2.0	2.0*	2.0*
- Exophtalmos	2.0	2.0	1.9	2.0	-
B. Secretion					
- Salivation	2.0	2.0	2.0	2.0	-
- Lacrimation	2.0	2.5	2.0	2.0	2.0
- Diarrhea	1.9	2.3	1.9	1.9	1.5
C. Miscellaneous					
- Hypothermia	2.0*	1.1	1.9	2.1*	2.0
- Piloerection	2.2	2.7	2.8	2.1	1.9
- Skin Color	2.0*	2.7	-	2.0*	2.0*
- Respiratory Rate	2.2	0.8	1.9	2.8	2.4

* Significant difference to the soman group (a _ 0.05)

Groups of 10 white NMRI mice received soman, 0.1 mg/kg s.c. or soman and immediately thereafter HI 6, 55 mg/kg or soman and atropine, 10 mg/kg, or soman, atropine and HI 6. Then the animals were allowed to run for 60 min on a rotating (14 rpm) mash wire drum (20 cm diam.). Before soman and after the running period the behavioral and physiologic state of the mice was quantified (arbitrary

units) according to Irwin (1968). Control animals received 0.9% NaCl solution s.c. and i.p. before the exercise.

Soman caused a decrease in plasma ChE activity by 47% (1,507 U/l) compared to control animals (3,188 U/l). A similar decrease in brain ChE activity was found (44%). HI 6 caused a recovery to 77% of control in the plasma but no change in the brain. No change was observed in atropine treated animals. Similar changes were observed with erythrocyte ChE activity.

The data presented show that soman does not impare spatial memory of mice up to about 50% of the LD_{50}. Higher doses might already cause serious physical symptoms which can disturb memory performance estimation.
Contrary to that, relatively low doses of soman, less than 10% of the LD_{50}, can cause an impairment of motor performance in mice. The impairment can be improved by atropine or HI 6 and its combination. The effects of the antidotes seem to be additive. Various parameters, measured in order to assess the behavioral and physiologic state of the animals, and changed by soman, exhibited a different pattern of sensitivity to the treatment with HI 6 or atropine. The differences are probably caused by a dissimilar mechanism of action and distribution of the drugs (CNS) in the organism.

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