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CHANGES IN ELECTROCORTICAL AROUSAL FOLLOWING ACUTE TRIMETHYLBENZENE ADMINISTRATION IN RATS

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Abstract. The purpose of this investigation was to compare the neurotoxic potential of trimethylbenzene (TMB) isomers (the solvents) with that of benzene derivatives with a smaller number of methyl groups (toluene). The experiments were performed on WAG/Rij rats with EEG recording electrodes implanted in the fronto-parietal cortex. The solvents, toluene or TMB isomers: 1,3,5-TMB (mesitylene), 1,2,3-TMB (hemimellitene) or 1,2,4-TMB (pseudocumene), were diluted with olive oil and administered intragastrically via gavage at an acute dose of 0.002, 0.008, or 0.032 mol/kg. The electrocortical activity was recorded for 20 min before, and for 60 min after the solvent administration. The electrocorticograms were analysed with respect to the number and duration of the high-voltage spindles (HVS), a form of activity sensitive to the arousal level. In case of each solvent the observed effect – inhibition of the HVS activity – was dose-related. However, the effect produced by TMB isomers was in each case less pronounced than that of toluene. Among TMBs, pseudocumene displayed the least significant effect, and the efficacy of two other TMB isomers was similar.

INTRODUCTION

Trimethylbenzene (TMB) isomers: pseudocumene (1,2,4 TMB), hemimellitene (1,2,3 TMB) and mesitylene (1,3,5 TMB) are substantial constituents of solvent mixtures used in the production of paints and lacquers. In some products available on the market their percentage contribution may exceede 40% (19). TMB can also be found in the composition of high-octane fuels (20). It is widely recognised that occupational exposure to industrial solvents may lead to long-term functional impairments of the central nervous system (CNS) (1,7,12). Owing to this fact, there is a need to find out whether, and to what extent TMB may contribute to the development of these impairments. At present, the literature data on neurotoxic effects of TMB exposure are not numerous as

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compared, for example, with those on neurotoxicity of xylene and toluene (4,5,6). Studies of acute inhalation exposure revealed that the respiratory irritative and neurotoxic effects of TMB isomers, assessed on the basis of the motor co-ordination and pain sensitivity tests, were stronger than those of toluene and xylene (9,10). Experiments on rabbits have revealed similar relations, indicating that pseudocumene exerts stronger effect on CNS than that of m-xylene, toluene and 4-ethylotoluene (16,17). The non-linear relationship between exposure level and behavioural effect is one of the features typical of acute solvent exposure. Low doses induce behavioural excitation, manifested by increased locomotor activity, whereas high doses result in behavioural depression. Both these effects are associated with the solvent concentration in blood. Therefore, changes observed after intragastric administration or after the onset of an inhalation exposure to high concentrations, are biphasic – an excitation phase turns into a depressive phase with a growing blood concentration of the solvent (11,14).

Our earlier studies (15) showed that the changes in the locomotor open field activity after intragastric administration of toluene at a dose of 0.008 mol/kg were biphasic. A dynamic increase of the locomotor activity lasting about 45 min was followed by its decrease. After a dose of 0.016 mol/kg, a biphasic character was less pronounced, and after a dose of 0.032 mol/kg a depressive effect was dominant. No similar pattern of changes was observed after administration of any of TMB isomers, and the values of consecutive measurements revealed that TMBs exerted much lower effect on locomotor activity than toluene. Parallel measurements of blood concentrations of the administered solvents showed that toluene yielded much higher values in comparison with TMB isomers administered at the same dose. These results suggest two possibilities. First, a slower, in comparison with toluene, absorption of TMBs from the alimentary tract, resulting in a weaker behavioural effect. Second, a faster, in comparison with toluene, diffusion of TMB from blood into target tissues, including the brain. In that case, the lack of apparent changes in locomotor activity could denote the dominating depressive effect even after the lowest dose used in the experiment. Death of some rats several hours after the administration of TMB isomers at the highest dose, and 100% survival among rats administered with toluene support the second possibility. It is known that the increase in behavioural excitation after the solvent administration is the consequence of its effect on the central nervous system. That is why we thought that the effects of solvents could be better assessed if we investigate the forms of the brain bioelectric activity sensitive to the arousal level.

In electrocorticograms of some rats, seizure activity in the form of spontaneous and intermittently occurring bursts of spike-wave discharges (SWD) develops with age (2). Bearing in mind characteristic changes in the SWD amplitude the bursts are sometimes referred to as high-voltage spindles (HVS) (18). The proneness to the HVS generation is a heritable trait (13). In some inbred rat strains, eg. the WAG/Rij strain used in the present study, the prevalence of this trait is 100% (2). Therefore the measurement of HVS number and duration after the solvent administration may provide direct information about the effect of a given solvent on the CNS functional state.

METHODS AND MATERIALS

Animals

The experiments were performed on 78 male rats of the WAG/Rij strain from our breeding colony, three to four months old and with body weights of 250–300 g. Food (standard rat Purina pellets) and water were provided *ad libitum*. The rats were housed in single rat cages at 22–25°C temperature, 55–60% humidity, with a dark/light cycle of 12/12 h. They were divided into five groups: four solvent groups (toluene, hemimellitene, psedocumene and mesitylene), each grup consisted of 18 rats, and the control oil group of 6 rats. In addition, each solvent group was subdivided into three dose subgroups, 6 rats per subgrup (0.002; 0.008; and 0.032 mol/kg). Before the experiment onset all rats had EEG recording electrodes implanted surgically. The experiments started 14 days after the operation.

Electrode implantation

The implantation of electrodes into the brain was performed using a stereotaxic instrument under general (pentobarbital sodium, 50 mg/kg i.p.) and local (1.0 ml of polocainum, s.c. into the wound area) anaesthesia. Two bipolar elctrodes, each made of two twisted strands of stainless steel teflon-coated wire, 200 μm in diameter (Medwire Corp.) were implanted bilaterally into the fronto-parietal cortex (2.0 mm lateral to the midsaggit suture and 2.0 mm anterior to Bregma) in such a way that the uninsulated (0.5 mm) tip of one strand penetrated the brain about 1.0 mm in depth and the second touched the cortical surface. A stainless steel jeweller screw (diam: 2.0 mm) fixed in the skull bone over the cerebellum, and a spiral made of silver wire placed under the skin on the nose bone, served as a reference electrode and ground, respectively. The outer ends of the electrodes were soldered to a miniature connector and the whole assembly was fixed to the skull with dental cement (Duracryl, SPOFA, Prague).

Chemical compounds and exposure conditions

In the experiment the following compounds were used: toluene (99.9%, CAS 108-88-3) supplied by POCH (Poland), and trimethylbenzene (TMB) isomers: 1,3,5-TMB (mesitylene, 99%, CAS 108-67-8); 1,2,4-TMB (psedocumene, 97%, CAS 95-63-6); and 1,2,3-TMB (hemimellitene, 90–95%, CAS 526-73-8) purchased from Fluka (Switzerland). The solvents were dissolved in olive oil and administered intragastrically via gavage at the doses of 0.002; 0.008; and 0.032 mol/kg b.w. in volume of 1.5 ml.

Electroencephalographic examinations

Bioelectric activity of the brain was recorded on an 8-channel electroencephalograph (ORMED Comp.), with time constant set at 0.3 s and high frequency filter set at 35 Hz. Prior to the recordings, animals were adapted for 15 min to the experimental situation. EEG was registered for 20 min before and for 60 min after administration of solvent. The recordings were analysed with regard to the number and duration of HVS episodes in the 20-min EEG sections denoted as S0 (preinjection control), S1, S2 and S3 (successive 20-min postinjection sections). A series of rhythmic, high-amplitude spike-and-wave discharges lasting not less than 1s was recognized as HVS (Fig. 1).

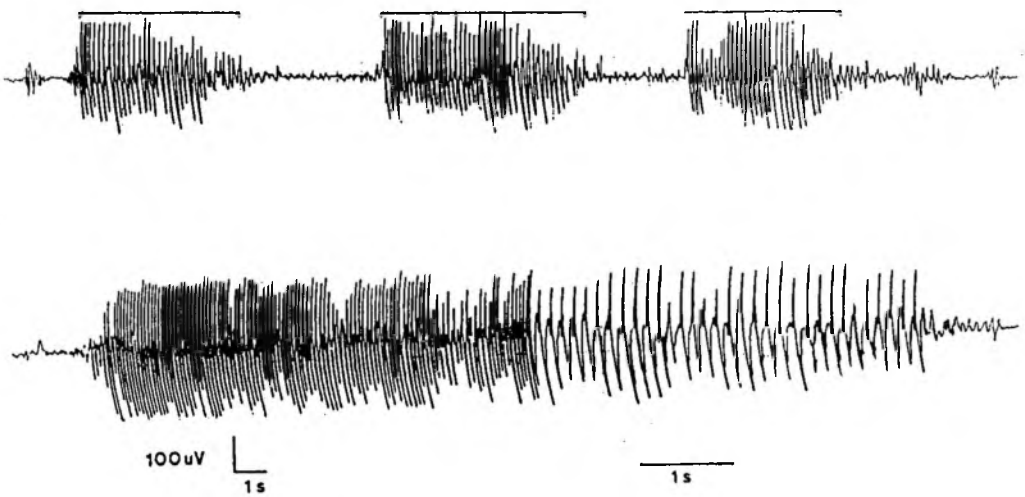

Fig.1. Fragments of rat electrocorticogram. Upper trace: fronto-parietal ECoG with high-voltage spindle (HVS) episodes (overlined). Lower trace: HVS activity recorded at 1 cm/s (left part) and 3 cm/s (right part) paper speed.

Statistical analysis

Data were analysed using repeated measures two-factor ANOVA (group × time, separately for each dose, and dose × time, separately for each group). The differences were regarded as significant when $p < 0.05$.

RESULTS

In general, after the injection of each solvent under study, at all doses applied, the duration (Fig. 2) and number (Fig. 3) of HVS episodes decreased. In case of toluene this effect was definitely stronger than that observed after administration of any of the TMB isomers. Among TMB isomers, hemimellitene appeared more potent then pseudocumene or mesitylene in the inhibition of HVS activity.

The solvent-response relationship

The total duration of HVS activity

A dose of 0.002 mol/kg. A statistical analysis indicated a significant effect of the group (compound) factor ($F(4,21) = 10.93$; $p < 0.001$, and the time factor ($F(1,21) = 10.71$; $p < 0.05$). The group-time interaction was also significant ($F(4,21) = 53.08$; $p < 0.001$). The comparisons of groups showed significant difference in S2 ($F(4,84) = 14.14$; $p < 0.001$) and S3 ($F(4,84) = 6.66$; $p < 0.001$). In S2, in all solvent groups, HVS duration was shorter than in the control group. In the toluene and hemimellitene groups, HVS duration was significantly shorter in S3 than in the control and psedocumene groups. The comparisons between successive EEG sections within each group, revealed significant differences in the psedocumene group ($F(3,63) = 7.69$; $p < 0.005$) and mesitylene group ($F(3,63) = 6.91$; $p < 00.5$). In the pseudocumene group, HVS duration was significantly shorter in S1 and S2, and in the mesitylene group in S1, S2 and S3 as compared to S0.

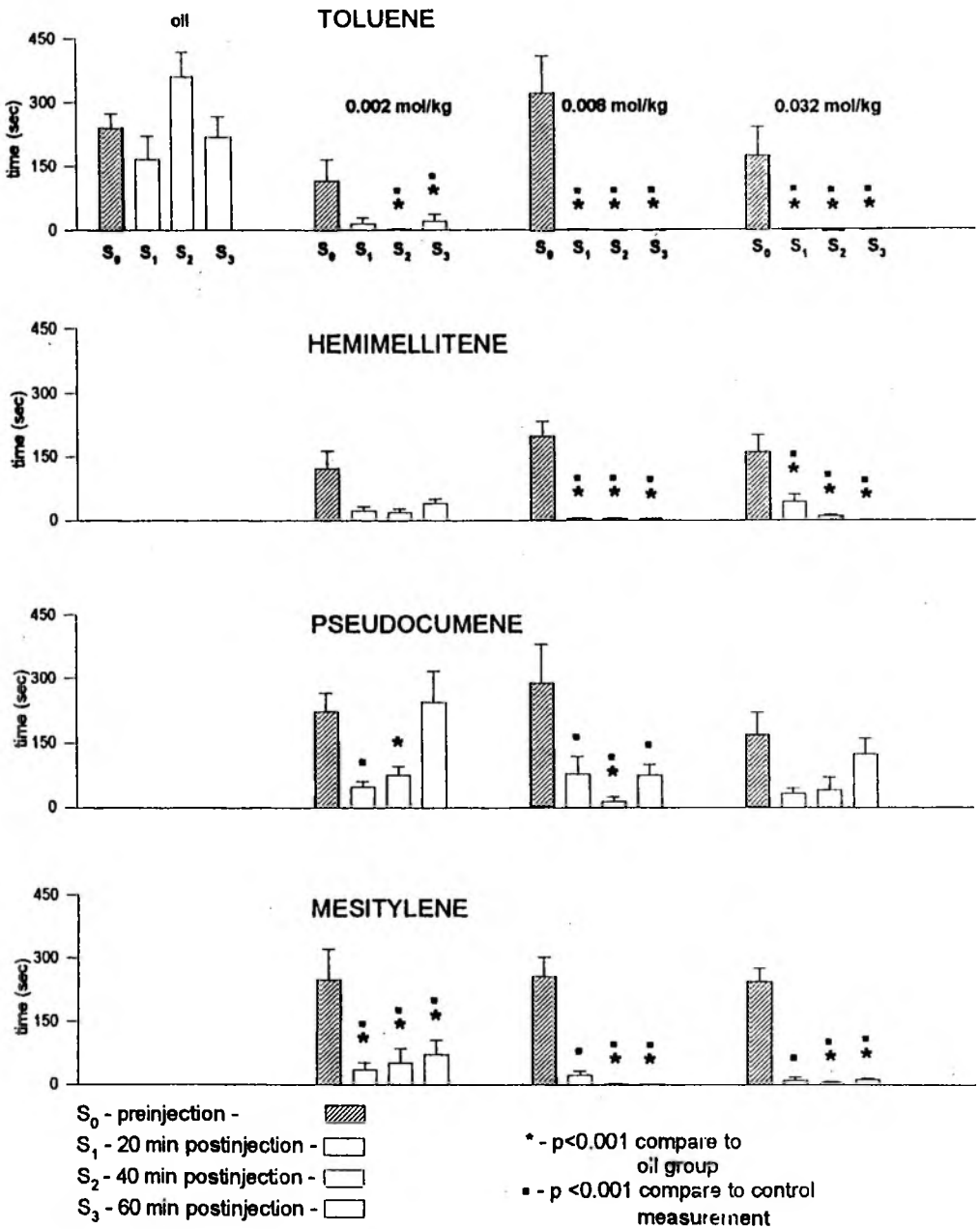

Fig. 2. Changes in total duration of HVS episodes following acute exposure to toluene and trimethylbenzene isomers, hemimellitene, pseudocumene and mesitylene at doses of 0.002 mol/kg, 0.008 mol/kg and 0.032 mol/kg.

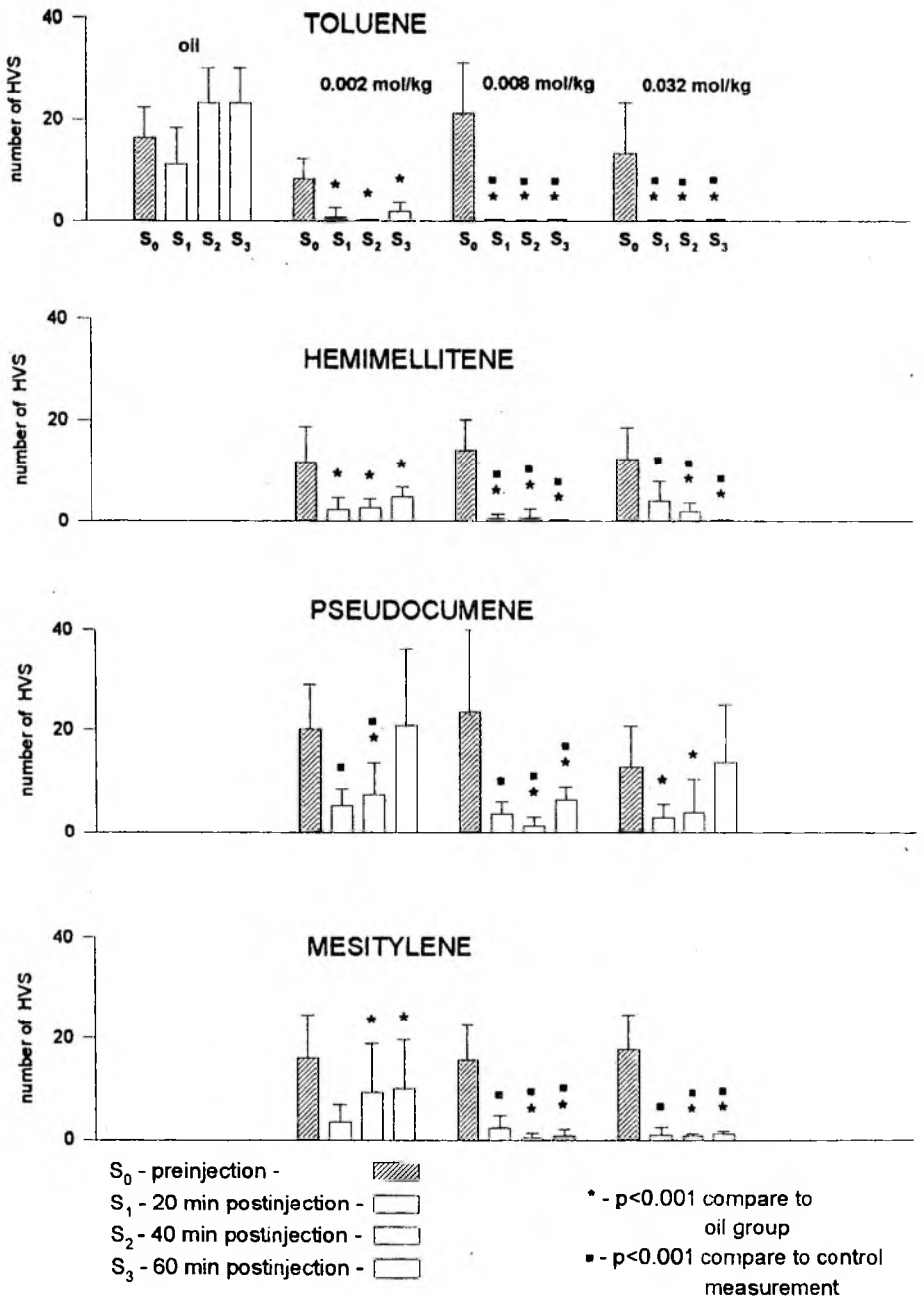

Fig. 3. Changes in the number of HVS episodes following acute exposure to toluene and trimethylbenzene isomers, hemimellitene, pseudocumene and mesitylene at doses of 0.002 mol/kg, 0.008 mol/kg and 0.032 mol/kg.

A dose of 0.008 mol/kg. An analysis of main effects revealed significant influence of the group factor ($F(4,22) = 13.36$; $p < 0.001$), and the time factor ($F(1,22) = 33.74$; $p < 0.001$). The group-time interaction was significant ($F(4,22) = 67.02$; $p < 0.01$). Between-group comparisons showed significant difference in S1 ($F(4,88) = 3.35$; $p < 0.01$), S2 ($F(4,88) = 17.65$; $p < 0.001$) and S3 ($F(4,88) = 6.18$; $p < 0.001$). In S1, HVS duration was significantly reduced in the toluene and hemimellitene groups and in S2 and S3 it was reduced in all solvent groups as compared to the control (oil) group. Within-group comparisons revealed significant differences in the toluene ($F(3,66) = 17.17$; $p < 0.01$), hemimellitene ($F(3,66) = 7.54$; $p < 0.01$), psedocumene ($F(3,66) = 10.51$; $p < 0.01$), and mesitylene ($F(3,66) = 9.97$; $p < 0.01$) groups. In each group all the postinjecton values (HVS total duration) were significantly smaller than the preinjection ones.

A dose of 0.032 mol/kg. A statistical analysis disclosed significant effect of the group factor ($F(4,24) = 20.94$; $p < 0.001$) and the time factor ($F(1,24) = 17.80$; $p < 001$). The significance of the interaction was also revealed ($F(4,24) = 55.50$; $p < 0.001$). The comparison between groups showed significant differences in S1 ($F(4,96) = 3.82$; $p < 0.001$), S2 ($F(4,96) = 20.55$; $p < 0.001$) and S3 ($F(4,96) = 8.12$; $p < 0.01$). The administration of toluene, pseudocumene and mesitylene reduced HVS duration in S2 and S3. Pseudocumene also reduced HVS duration as compared to the oil group. The comparisons of HVS duration at individual time points, made separately for each group, revealed significant differences with regard to toluene ($F(3,72) = 6.75$; $p < 0.001$), hemimellitene ($F(3,72) = 4.71$; $p < 0.001$), psedocumene ($F(3,72) = 3.93$; $p < 0.001$), and mesitylene ($F(3,72) = 10.28$; $p < 0.001$). Toluene reduced HVS duration at all time points, hemimellitene in S2 and S3, psedocumene in S1 and S2, and mesitylene at all the time points as compared to S0.

The number of HVS episodes

A dose of 0.002 mol/kg. An analysis showed statistical significance of the group factor ($F(4,21) = 9.82$; $p < 0.001$), the time factor ($F(1,21) = 14.52$; $p < 0.01$) and the group × time interaction ($F(4,21) = 44.22$; $p < 0.01$). The comparison between groups at each time point revealed significant differences in S2 ($F(4,84) = 9.90$; $p < 0.001$), and S3 ($F(4,84) = 10.11$; $p < 0.001$), although in S3 the number of HVS episodes after the injection of mesitylene was larger than that after the administration of toluene and hemimellitene. The comparisons between individual time points, made separately for each group, revealed significant differences with regard to pseudocumene ($F(3,63) = 10.01$; $p < 0.001$. In S1 and S2 a decrease in the number of HVS episodes was observed as compared to S0.

A dose of 0.008 mol/kg. An analysis showed statistical significance of the group factor ($F(4,22) = 17,49$; $p < 0.001$) and the time factor ($F(1,22) = 29.84$; $p < 0.001$). The group × time interaction was significant ($F(4,22) = 72.51$; $p < 0.001$). The comparisons between individual groups at each time point revealed significant differences in S1 ($F(14,88) = 2.90$; $p < 0.05$), S2 ($F(4,88) = 14.67$; $p < 0.001$) and S3 ($F(4,88) = 13.89$; $p < 0.001$). In comparison with the control group, a significantly smaller number of HVS episodes was noted in S1 after the administration of hemimellitene and toluene. The comparisons between individual time points made for each group revealed significant differences after the administration of toluene ($F(3,66) = 14.34$; $p < 0.001$), hemimellitene ($F(3,66) = 8.33$;

$p < 0.001$), pseudocumene ($F(3,66) = 13.20$; $p < 0.001$), and mesitylene ($F(3,66) = 6.84$; $p < 0.001$). The number of HVS episodes at each time point was reduced comparing with S0.

A dose of 0.032 mol/kg. An analysis showed statistical significance of the group factor ($F(4,24) = 22.19$; $p < 0.001$) and the time factor ($F(1,24) = 16.88$; $p < 0.001$). The group × time interaction was significant ($F(4,24) = 68.86$; $p < 0.001$). The comparisons between individual groups at each time point revealed significant differences in S1 ($F(4,96) = 3.15$; $p < 0.01$), S2 ($F(4,96) = 15.61$; $p < 0.001$) and S3 ($F(4,96) = 17.48$; $p < 0.001$). In S1 only the administration of toluene reduced the number of HVS episodes; in S2 each of the groups injected diminished the number of HVS episodes; and at time point 4 the number was reduced by toluene, hemimellitene and mesitylene. Within-time point comparison made for each group revealed significant differences after the administration of toluene ($F(3,72) = 7.54$; $p < 0.001$), hemimellitene ($F(3,72) = 5.03$; $p < 0.001$), psedocumene ($F(3,72) = 15.64$; $p < 0.001$), and mesitylene ($F(3,72) = 10.17$; $p < 0.001$). Toluene and mesitylene reduced the number of HVS episodes at each time point and hemimellitene in S2 and S3 as compared to S0.

The dose-response relationship

The total duration of HVS activity

Toluene. An analysis showed statistical significance of the group factor ($F(3,18) = 18.45$; $p < 0.01$) and the time factor ($F(1,18) = 15.19$; $p < 0.001$).The administration of toluene at all doses reduced the duration of HVS episodes as compared to the oil group. The reduction in duration time was significant at each time point. The dose × time interaction was also significant ($F(3,18) = 41.30$; $p < 0{,}001$).The comparison between doses at each time point indicated significant differences in S1 ($F(3,72) = 4.32$; $p < 0{,}01$, S2 ($F(3,72) = 21.03$; $p < 0.01$) and S3 ($F(3,72) = 7.42$; $p < 0.01$). At these time points toluene injected at the doses of 0.008 and 0.032 mol/kg reduced the duration of HVS episodes in comparison with the oil group. In addition, the reduction in duration time was observed in S2 and S3 after the administration of toluene at a dose of 0.002 mol/kg. Within-time points comparisons revealed significant differences at the doses of 0.008 and 0.032 mol/kg. In both cases the reduction in HVS duration was observed at each time point after the injection of the group as compared to S0.

Hemimellitene. An analysis of the main effects showed significant effect of the group factor ($F(3,19) = 27.69$; $p < 0.01$) and the time factor ($F(1,19) = 40.46$; $p < 0.001$). In comparison with the oil group, hemimellitene reduced HVS time at each dose. The reduction in HVS duration was evident at all time points. The dose × time interaction was significant ($F(3,19) = 40.62$; $p < 0.001$). The comparison between doses at each time point indicated significant differences in S1 ($F(3,76) = 5.55$; $p < 0{,}001$, S2 ($F(3,76) = 31.30$; $p < 0.001$) and S3 ($F(3,76) = 11.31$; $p < 0.001$). Hemimellitene injections at all the three doses reduced HVS duration as compared to the control group. Within-time point comparisons indicated significant differences at a dose of 0.008 mol/kg ($F(3,57) = 11.33$; $p < 0.001$), and at a dose of 0.032 mol/kg ($F(3,57) = 6.25$; $p < 0.01$). In both cases hemimellitene injections reduced HVS duration at each time point as compared to S0.

Psedocumene. An analysis showed significant effect of the group factor ($F(3,18) = 6.93$; $p < 0.05$) and the time factor ($F(1,18) = 8.09$; $p < 0.01$). Pseudocumene injections at all the three doses reduced HVS time when compared with the control group. The dose × time interaction was significant ($F(3,18) = 31.43$; $p < 0.001$). The comparison of doses at each time point revealed significant differences in S2 ($F(3,72) = 12.83$; $p < 0.001$. The injection of the solvent at each dose reduced HVS duration. Within-time point comparisons at all doses in question disclosed significant differences at the 0.002 and 0.008 mol/kg doses ($F(3,54) = 4.94$; $p < 0.001$) and ($F(3,54) = 7.12$; $p < 0.01$), respectively. In comparison with the control measurement, the reduction in HVS duration was observed in the 0.002 mol/kg group in S1 and in the 0.08 mol/kg group at all time points.

Mesitylene. An analysis showed significant effect of the group factor ($F(3,17) = 14.08$; $p < 0.001$) and the time factor ($F(1,17) = 21.60$; $p < 0.001$). Each dose of mesitylene reduced HVS duration. The dose x time interaction was significant ($F(3,17) = 41.92$; $p < 0.001$). The comparison of doses at each time point revealed significant differences in S1 ($F(3,68) = 3.87$; $p < 0.01$, S2 ($F(3,68) = 21.53$; $p < 0.01$) and S3 ($F(3,68) = 7.30$; $p < 0.01$). In S1 the reduction in HVS duration was observed after the injection of the 0.002 mol/kg dose. In S2 and S3, each dose reduced HVS duration as compared to the control group. Within-time point comparisons made for each dose separately disclosed significant differences at the doses of 0.002 mol/kg ($F(3,51) = 7.32$; $p < 0.01$), 0.008 mol/kg ($F(3,51) = 11.69$; $p < 0.001$) and 0.032 mol/kg ($F(3,51) = 10.45$; $p < 0.001$). After the injection, the reduction in HVS duration was observed at all doses and at all time points as compared to S0.

The number of HVS episodes

Toluene. An analysis showed significant effect of the group factor ($F(3,18) = 35.33$; $p < 0.001$) and the time factor ($F(1,18) = 17.15$; $p < 0.001$). The injection of toluene at each dose reduced the number of HVS episodes in comparison with the oil group. The reduction in the number of HVS episodes was evident at each time point. Within-group comparisons at each time point showed significant differences in S1 ($F(3,72) = 5.42$; $p < 0.01$, S2 ($F(3,72) = 24.68$; $p < 0.001$) and S3 ($F(3,72) = 23.04$; $p < 0.001$). After the injection of toluene the reduction in the number of HVS episodes was noted at all the three doses and at all time points. Within-time point comparisons in each group disclosed significant differences after the injection of toluene at the doses of 0.008 mol/kg ($F(3,54) = 18.08$; $p < 0.001$), and 0.032 mol/kg ($F(3,54) = 8.51$; $p < 0.01$). In both cases the number of HVS episodes was diminished at each time point as compared to the control measurement.

Hemimellitene. An analysis showed significant effect of the group factor ($F(3,19) = 36.87$; $p < 0.001$) and the time factor ($F(1,19) = 13.78$; $p < 0.01$). The administration of hemimellitene reduced the number of HVS episodes in all groups in comparison with the oil group. The reduction in the number of HVS episodes was marked at each time point after the administration of hemimellitene as compared to the control measuremensts. The dose × time interaction was significant ($F(3,19) = 48.33$; $p < 0.001$). Within-group comparisons at each time point showed significant differences in S1 ($F(3,76) = 4.89$; $p < 0.01$, S2 ($F(3,76) = 25.87$; $p < 0.001$) and S3 ($F(3,76) = 26.76$; $p < 0.001$). At each of these time points the administration

of hemimellitene at the doses of 0.002 and 0.008 mol/kg reduced the number of HVS episodes as compared to the oil group. A similar effect was observed in S2 and S3 after hemimellitene injection at a dose of 0.002 mol/kg. Within-time point comparisons in each group disclosed significant differences at the doses of 0.008 mol/kg ($F(3,57) = 11.11$; $p < 0.001$), and 0.032 mol/kg ($F(3,57) = 6.98$; $p < 0.01$). In both cases, the number of HVS episodes was diminished at each time point as compared to the control measurements.

Pseudocumene. A statistical analysis showed significant effect of the group factor ($F(3,18) = 4.70$; $p < 0.01$) and the time factor ($F(1,18) = 11.18$; $p < 0.01$). The administration of pseudocumene at the doses of 0.008 and 0.032 mol/kg decreased the number of HVS episodes as compared to the oil group. In S1 and S2 the number of HVS episodes was smaller than in the control measurements. The dose × time interaction was significant ($F(3,18) = 27.02$; $p < 0.001$). The comparison between doses at each time point revealed significant differences in S2 ($F(3,72) = 7.71$; $p < 0.001$) and S3 ($F(3,72) = 4.14$; $p < 0.01$). In S2 the reduction in the number of HVS episodes was noted after the administration of pseudocumene at all the three doses as compared to the oil group. In S3, the administration of the solvent at a dose of 0.008 mol/kg reduced the number of HVS episodes as compared to the oil group and the 0.002 mol/kg group. Within-time point comparisons made for each group disclosed significant differences at the doses of 0.002 and 0.008 mol/kg ($F(3,54) = 5.66$; $p < 0.01$, and $F(3,54) = 8.52$; $p < 0.001$, respectively). Pseudocumene at a dose of 0.002 mol/kg decreased the number of HVS episodes in S1 and S3, and at a dose of 0.008 mol/kg at all time points as compared to the control measurement.

Mesitylene. A statistical analysis showed significant effect of the group factor ($F(3,17) = 16.50$; $p < 0.001$) and the time factor ($F(1,17) = 15.39$; $p < 0.01$). The injection of mesitylene decreased the number of HVS episodes in all groups as compared to the oil group and the reduction was marked at each time point in comparison with control measurements. The dose × time interaction was significant ($F(3,17) = 43.65$; $p < 0.001$). Within-group comparisons at each time point showed significant differences in S2 ($F(3,68) = 17.14$; $p < 0.001$ and S3 ($F(3,68) = 15.87$; $p < 0.001$). In both cases, the injection of mesitylene at all the three doses reduced the number of HVS episodes as compared to the oil group. Within-time point comparisons made for each group disclosed significant differences at the doses of 0.008 and 0.032 mol/kg ($F(3,51) = 8.04$; $p < 0.01$, and $F(3,51) = 10.84$; $p < 0.001$, respectively). In both cases, postinjection reduction in the number of HVS episodes occurred at each time point as compared to the control measurement.

DISCUSSION

The former observations (15) indicated that the changes in locomotor activity in rats after intragastrical administration of the same solvents were biphasic with regard to toluene. But contrary to our expectations, behavioural effects of TMB appeared to be much less pronounced than those of toluene injected at the same doses, while a biphasic character of changes in locomotor activity was not clearly marked. It seems that these results are not in agreement with the data, obtained by Korsak and Rydzyński (10), suggesting higher neurotoxicity of TMB as compared to toluene and xylene. None of the results at the present stage of investigations

confirmed the higher neurotoxic potential of TMB than that of toluene. The presence of the dose-response relationship in the case of each solvent deserves special mention. The least pronounced effect on a given parameter was exerted by the lowest dose. However, the data from the analysis showed that toluene injected even at the lowest dose among those applied (0.002 mol/kg) evidently inhibited HVS activity. From among TMB isomers, administered at the same dose, hemimellitene was found to exert the most extensive inhibitory effect on HVS activity, and its higher doses (0.008 and 0.032 mol/kg) totally eliminated this activity. TMBs administered at the same doses also suppressed HVS activity, but they did not inhibit it completely; in respect to seudocumene, HVS activity returned to the normal level within 1 h after injection. EEG changes suggested that toluene exerted most and psedocumene least marked effect on HVS activity. The efficacy of mesitylene and hemimellitene was similar.

In rats not given any of these groups HVS episodes occurred primarily at rest. An increase in behavioural and encephalographic arousal (disynchronisation in cortical record and occurrence of theta rhythm in hippocampus leads) goes together with the decline in HVS activity. But HVS activity also declines at slow-wave and REM sleep (3,8). Thus, the decrease in HVS activity may occur not only when behavioural excitation is increasing but also when it is falling. This may raise the question on whether the changes in HVS activity, observed in the studies described here, result from the excitation increase or decrease. Based on the results from the previous experiment (15), it could be thought that in respect to toluene, administered at the doses of 0.002 and 0.008 mol/kg, the decrease in HVS activity was associated with the increase in the level of behavioural excitation. The same effect after a dose of 0.032 mol/kg could be related to deep arousal fall (drug-induced sleep). As to TMB, the answer to this question is even more difficult. But regardless of the causes of HVS activity suppression – excitation increase or decrease – the range of the changes following TMB injection was much smaller than that induced by toluene. This is supported by the fact that, as opposed to toluene, none of TMB isomers suppressed completely HVS activity after injection. Our results suggest that the effect of TMB isomers on the arousal level, assessed on the basis of locomotor activity and spontaneous cortical seizures, is much less pronounced than that of toluene. Of the three TMB, pseudocumene exerts the weakest effect, and the efficacy of two others is similar.

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