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A Comparison of the Effects of Individual Organic Solvents and Their Mixture on Brain Stimulation Reward

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YAVICH, L. AND E. ZVARTAU. *A comparison of the effects of individual organic solvents and their mixture on brain stimulation reward.* PHARMACOL BIOCHEM BEHAV **48**(3) 661–664, 1994. – In spite of the prevalence of solvent abuse, there are only a few experimental investigations on the addictive potential of household organic solvents. In the present study we attempted to investigate the influence of glue thinner, a very popular glue used by glue-sniffing children, and the four organic solvents that compose this thinner (toluene, mixture of petroleum hydrocarbons, ethyl acetate, methylene chloride) on self-stimulation of the lateral hypothalamus (ICSS) in rats. Glue thinner, toluene, a mixture of petroleum hydrocarbons, and methylene chloride had a biphasic effect on ICSS, increasing frequency of self-stimulation at lower concentrations and decreasing it at higher concentrations. Ethyl acetate decreased frequency of self-stimulation at all concentrations. In contrast to classically abused drugs, solvents increased the threshold current of self-stimulation. The differences between concentration-response curves of ICSS for glue thinner and solvents permit the proposal that the mixture of solvents can be more dangerous than the individual components in potential for inducing solvent abuse.

Organic solvent Glue thinner Intracranial self-stimulation Rat

AN epidemic of inhalant abuse in children and juveniles has taken place in recent years in nearly all industrialized countries. However, at present no experimental evaluation of the addictive potential of different organic solvents and their mixtures precedes their marketing as household chemical products. We consider this to be a rather alarming factor when one compares the situation with narcotic drugs used in medicine which are strictly controlled by the authorities. Thus, in spite of reliably established hygienic norms, organic solvents occupy an exceptional position in being regarded as socially dangerous. It is important to note that glue sniffers have distinct preferences from the many solvents available, and only certain products are abused at epidemic proportions. For example, since about 1986, a glue solvent, the so-called Moment thinner, has been sniffed by St. Petersburg children and more than 80% incidents of acute intoxication which required medical assistance were due to intoxication with Moment thinner (A. Kuzmin, Main Administration of Public Health, personal communication). In addition, an epidemic of inhalant abuse was observed in Berlin in the mid 1970s with the glue "Pattex" (Henkel, Germany) (1,2) which was a prototype for the glue Moment in Russia.

The differences in behavioural effects of various solvents have been elucidated. For example, most investigated solvents predominantly produce biphasic effects on operant behaviour [(11,12); for a review see (7)]. At the same time some ketones (3,12) and halogenated hydrocarbons (5,6) only cause rate-decreasing effects on schedule-controlled responding. It seems probable that the preferences of glue sniffers for certain types of household chemical products could be based on the differences in their addictive properties.

A comparison of the effects of solvents and their mixture (Moment thinner) on the brain reward system was used to reveal these differences.

MATERIALS AND METHODS

Male mixed-breed albino rats (200–250 g) were used. The animals were kept under a 12-h light-dark cycle and had free access to water and food. The glue, "Moment-1" (ERA, Russia), contains four organic solvents: toluene 25%, a mixture of petroleum hydrocarbons (benzine fraction) 37%, ethyl acetate 31%, and methylene chloride 7%. Inhalation (static exposure) of Moment thinner and each solvent were performed in a

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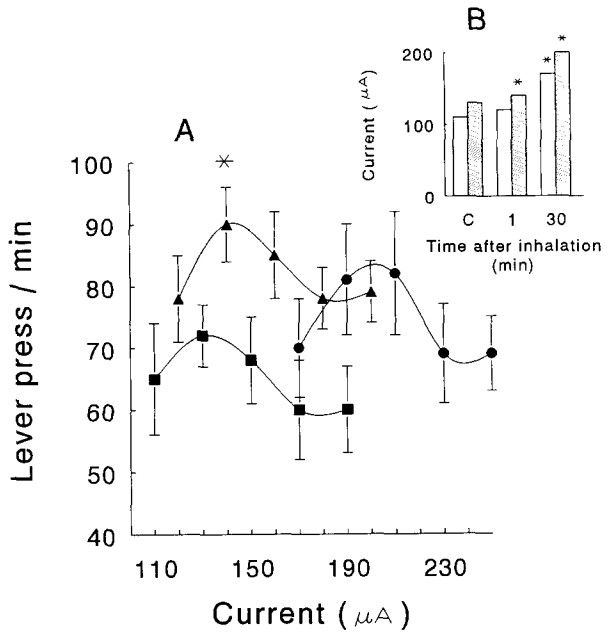

FIG. 1. Effects of Moment thinner (7200 ppm) on self-stimulation of the lateral hypothalamus (ICSS) response rate and current of stimulation. (A) Curves of response rate-current dependence. ■, before inhalation; ▲, 1 min after inhalation; ●, 30 min after inhalation. The symbols are the means ± SEM (n = 8). Statistical comparison of ICSS frequency was made at the levels of threshold and optimal current. *$p < 0.05$ vs. control, t test. (B) Threshold (open bars) and optimal (dotted bars) current of ICSS, measured before (C) and 1 min and 30 min after inhalation. *$p < 0.05$ vs. control, t test.

hermetic chamber with a capacity of 60 l at room temperature. No more than five animals were housed simultaneously in the chamber over a reservoir with a capacity of 2 l. The desired concentration was generated during 3 h by evaporation of a thin glue layer or individual organic solvents with calculated volume poured over a glass plate. The concentration of individual solvents in ppm was calculated by means of the ideal gas law, assuming normal atmospheric conditions. The molecular weight of the benzine fraction was estimated as an average molecular weight of its main components (89.6). The concentrations of glue vapours were established on the base of preliminary experiments in which, first, an average weight of the evaporated solvents was calculated for six samples of the glue with known weight poured over a glass plate. In this experiment the weight loss of 50 ± 3% (mean ± SEM, n = 6) was established in 3 h of evaporation of the glue. Second, the desired concentration of glue vapours in ppm was calculated with regard to the percentage of the glue evaporation, specific gravity of the glue, and molecular weights of the solvents which constitute the thinner. Finally, two samples of the atmosphere in the chamber were analysed at the beginning and at the end of the inhalation period by gas chromatography. The differences between these two measurements did not exceed 10% for all solvents, and proportions between the solvents which constitute the thinner remained stable. The inhalation time lasted 60 min in all experiments. Each animal was tested no later than 60 s after the inhalation period.

The influence of solvent vapour on brain stimulation reward was studied by means of the method of intracranial self-stimulation (ICSS). Rats were implanted (under pentobarbital anaesthesia, 60 mg/kg IP) with electrodes into the medial forebrain bundle area of the lateral hypothalamus. The coordinates for the stimulation electrodes were 2.5 mm posterior to bregma, 1.5 mm off the midline, and 8.5 mm below the surface of the cortex. After six days of postoperative recovery and four to five days of training the animals were tested in five consecutive trials each 1 min in duration. Parameters of rectangular impulses in all experiments were as follows: duration, 2 ms; period, 10 ms; duration of stimulation on each lever press, 300 ms. During the first trial a threshold current was determined as the lowest current which induced and maintained ICSS for at least 1 min. In every following 1-min trial the current was increased by 20 μA and the number of lever presses was recorded automatically. The animals were tested before and 60 s and 30 min after inhalation. The effects of each concentration of Moment thinner (taken in randomised order) were investigated with two-day intervals in eight rats. Each concentration of individual solvents was studied in five animals. For statistical analysis the t test was used.

RESULTS

Inhalation of Moment thinner at a concentration of 7200 ppm produced changes in parameters of ICSS. Immediately following the inhalation, the ICSS frequency was increased (Fig. 1A). The threshold current also displayed a similar tendency. The optimal current at which maximal ICSS frequency was recorded increased by 10 μA (Fig. 1B). Thus, the current-frequency curve was shifted upwards and to the right. Thirty minutes after the inhalation a further increase of the ICSS threshold and optimal current was observed. The ICSS frequency decreased (i.e., the curve current-frequency shifted further to the right and down). Increasing the concentration

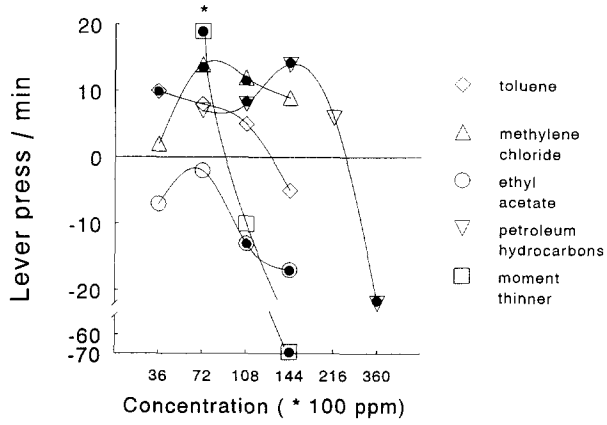

FIG. 2. Comparison of the effects of organic solvents on self-stimulation of the lateral hypothalamus (ICSS) response rate. Ordinate: changing of ICSS frequency from baseline. Each curve represents concentration-response dependence, measured at optimal current (i.e., at the current which induced a maximal response). The symbols are the means (five rats for individual solvent and eight rats for Moment thinner). Filled symbols show significant differences vs. baseline. Statistical comparison of ICSS frequency between solvents and Moment thinner was made at the level of maximal responses. *$p < 0.05$, Moment thinner vs. each individual solvent at maximal response, t test.

of the vapours to 10 800 ppm produced no significant changes in ICSS parameters (data not shown). When Moment thinner was inhaled at a concentration of 14 400 ppm, the ICSS was completely suppressed even at maximal intensity of electrical stimulation. A recovery time of 30 min was required to restore the initial frequency at the optimal stimulation current.

The solvents which make up Moment thinner were investigated the same way, but we did not analyze the effects of each solvent 30 min after inhalation. It was found that the four investigated solvents increased threshold of ICSS similar to Moment thinner itself. Nevertheless, this effect was neither dose-dependent nor significantly different between the solvents (data not shown). Since solvents like Moment thinner did not affect the shape of the current–frequency curves and only shifted them, the concentration–response curves for each solvent are shown at the optimal current (Fig. 2). The solvents, except ethyl acetate, increased frequency of ICSS at lower concentrations and either decreased it (mixture of petroleum hydrocarbons) or did not affect this parameter (toluene, methylene chloride) at higher concentrations. Ethyl acetate had no effect on the ICSS at lower concentrations, and decreased frequency of ICSS at higher ones.

DISCUSSION

The main findings of the present work are 1) there is a concentration-dependent biphasic effect of Moment thinner and organic solvents on the frequency of ICSS, and 2) there are differences between the effect of individual solvents and their mixture on the brain reward system.

Moment thinner significantly increased ICSS frequency. The increase of ICSS frequency and decrease of stimulation threshold are typical effects of drugs with addictive potential (14). Another well-known effect of drugs having abuse potential is their self-administration. This effect has also been demonstrated for organic solvents (19,20). Thus, the properties of organic solvents in these models are similar to those of classic abused drugs. Recently, it has been shown that basal extracellular dopamine level in striatum was increased during and after exposure to a low concentration (2000 ppm, 2 h) of toluene, while basal acetylcholine level was not affected and the concentration of GABA decreased (16). Since dopaminergic modulation of ICSS is a well-established fact (8,17), we assume that the increase of ICSS frequency induced by organic solvents may be related to their neurochemical effects. However, solvents increased the threshold of ICSS, and this seems to be one characteristic which differentiates organic solvents from other drugs with abuse potential. This finding may reflect "nonspecific" inhibitory processes in the CNS which dominate at higher concentrations of the solvent. We suggest this because the effect bore no correlation with the concentration and the threshold was enhanced 30 min after inhalation when the concentration of solvent in the blood was very low compared to initial levels (4,9).

Moment thinner and its components, except ethyl acetate, had a biphasic effect on ICSS. It is known that the dose–response curve for many abused drugs in many behavioural tests has an inverted U-shape form. Low doses increase locomotion, frequency of ICSS, and other reward-related behaviours, and higher doses reduce behavioural responses (10, 13,15). A similar biphasic effect has been shown for self-administration of toluene (18). Thus, the rate-increasing effect of solvents seems to be an important indicator of their abuse potential. Moment thinner had the highest rate-increasing effect in ICSS. On the other hand, a lower concentration of Moment thinner was required to totally block ICSS in comparison to its individual components. It is tempting to conclude that the mixture of solvents is more effective at activating brain reward systems than each solvent on its own, and that ethyl acetate had minimal reward properties. Indeed, these results and proposals should be compared to those from other evaluations of abuse potential such as self-administration and drug discrimination tests.

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