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Effects of Phenylmercury Acetate on Motor Behaviors and Other Physiological Functions in Mice

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Phenylmercury acetate (PMA) was given by single subcutaneous (SC) administration in adult male mice at doses of 7.5, 15, 22.5, and 30 (mg/kg), respectively. The mice were then observed for 21 days. Rotarod performance and multivariate locomotor behaviors of mice were tested on the rotarod treadmill and with the Digiscan system at 1st day, 2nd day, 3rd day, 1st week, 2nd week and 3rd week, respectively. PMA at dose of 30 mg/kg significantly decreased stereotypy behaviors (stereotypy time, stereotypy counts, and stereotypy number). PMA at doses of 22.5 mg/kg and 30 mg/kg markedly decreased rotarod performance and urination on the 1st, 2nd, and 3rd day after administration of PMA. In addition, PMA was found to decrease body weight and cause death in mice in a dose-dependent manner. Since PMA significantly decreased the concentration of DOPAC in the limbic area and attenuated the potential of integral electromyograph (IEMG) in rectus femoris muscle in mice, the results appear to show that PMA decreases the number of stereotypy behaviors and that rotarod performance maybe include both central and peripheral sites. Therefore, we tentatively assumed that the neurotoxic sites of PMA include the mesolimbic dopaminergic pathway and the cholinergic pathways at least.

Key words: Phenylmercury acetate, motor behaviors, mice.

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Introduction

Mercury occurs as elemental mercury and as inorganic and organic compounds: mercury vapor, mercury liquid, mercury salts short-chain alkylmercury compounds, alkoxyalxlmercury compounds and phenylmercury compounds, all having different toxicological properties. It is circulated naturally in the biosphere, 30,000-150,000 tons being released into the atmosphere by the degassing of the earth's crust and the oceans. In addition, 20,000 tons of mercury is released into the environment each year by such human activities as the combustion of fossil fuels and other forms of industrial release. Yearly, 10,000 tons of mercury is produced for industrial use, a small part of which is used for synthesizing organic mercury compounds. From the toxicological point of view, inorganic and organic mercury compounds exhibit differential toxic effects on various tissues. Because organic mercury can be degraded into inorganic mercury by singlet oxygen, which is generated from seawater exposed to sunlight [1], and because it can also be reversibly converted from inorganic mercury as a consequence of microbial metabolism and/or sunlight activity [2,3], the coexistence of both inorganic and organic mercury compounds can be found in mercury-polluted environments.

Phenylmercury acetate is a kind of organomercury compound used widely in agriculture in various pesticides and fungicides [4,5], in latex paint preservatives [6-8], in contraceptives as a spermicidal [9], in cosmetics, ophthalmic solutions, shampoos, shoe linings, laundry detergents and dental amalgams [10]. PMA has been reported to cause acrodynia and contact urticaria syndromes in humans [8,11] and induce genotoxicity in mammalian cells [12-14]. However, little research has been done on the effects of PMA exposure on the locomotor behavior in small laboratory animals such as mice, whose neurobehavioral changes can be observed to determine the toxic effects of chemicals [15-17]. Of these changes, motor activity in familiar or unfamiliar surroundings is the most frequently measured variable, because of its high sensitivity to toxic hazards. Additionally, the toxic effects of PMA on other physiological functions in mice have not been studied in as much detail as they have been with mercuric salts. Therefore, in this study besides observing the effects of PMA on the locomotor behavior in mice, we also investigated the effects of PMA on their urination, death, and body weight.

Materials and Methods

Fifty adult male mice (ICR strain) with a body weight of 22 to 26 g were obtained from the animal center of National Taiwan University, and provided with a solid diet and tap water ad libitum. Room temperature was 25 $\pm$ 1°C, relative humidity was 55 $\pm$ 10%, and dark/light cycles lasted 12 h each (lights on from 07:00$\sim$ 19:00). A continuous white noise of 50-60 dB was used to mask extraneous sounds. The mice were divided into five tests groups with 10 mice each (1 control group and 4 PMA treatment groups). Prior to PMA treatment there was no significant statistical difference in body weight or difference in locomotor behavior among each group. Phenymercury acetate (PMA), purchased from Merck Co., was dissolved in dimethyl sulfoxide (DMSO). The 10 mice in each of the 4 PMA treatment groups and control group received a single subcutaneous injection of 7.5 mg/kg, 15 mg/kg, 22.5 mg/kg, 30 mg/kg PMA, and 0.1% DMSO, respectively. They were then continuously fed for 3 weeks. The investigations of rotarod performance with some modification as described below were carried out according to Kuribara et al. [18], and observations of multi-

variate locomotor behavior were done according to Sanberg et al. [19].

Rotarod Performance: To test the effect of PMA on compulsive motor behavior, we used a rotarod treadmill for mice (Ugo Basile, Italy). A plastic rod, which was 3 cm in diameter, 30 cm long with no slippery surface and 15 cm over the base, was divided into 5 equal sections by 6 discs, enabling 5 mice to walk on the rod at the same time. In this study, we only used a rotarod treadmill speed of 14 r.p.m. to measure performance. The time each mouse remained on the rod was recorded in seconds. At 900 seconds, all remaining mice were removed. The training of the mice for the rotarod test was done the day before, and animals who performed on the rod for more then 360 sec were used for the assay.

Multivariate locomotor behaviors: The test for the effect of PMA on spontaneous motor activity (SMA) was conducted by placing the animals in an open field under a 100 watt light. Total ambulatory distance (cm), horizontal activity (cm); move time (sec), vertical activity (cm), vertical time (sec), Stereotypy count (cm), and stereotypy time (sec) were automatically measured by the Digiscan system (Omnitech). All multivariate locomotor behaviors were recorded for a 3-min period.

HPLC assay of DOPAC: The mice were treated with PMA (30 mg/kg) and killed by decapitation at first day after PMA treatment. Brains were rapidly excised, the limbic area (including tuberculus olfactorium and nucleus accumbens) was dissected, frozen on dry ice and kept at -80℃ until biochemical assay. The DA metabolites, DOPAC, were determined in the striata of one mouse. Tissues were homogenized with a sonifier in 300 μl of 0.4 N perchloric acid and centrifuged. The clear supernatant was used for the DOPAC assay according to a method previously described by this laboratory [20]. Liquid chromatography with electrochemical detection waters was used for biochemical determinations [21].

Integral electromyograph (IEMG) measurement: Tests for the effect of PMA (30 mg/kg) on IEMG in mice were made as previously described [22]. The first day after PMA treatment, the mice were fixed onto the board and two needle electrodes were inserted into the rectus femoris muscle of left hind limb. The distance of two record electrodes was 0.5 cm. The reference electrode was inserted into the triceps muscle of left forelimb. Direct stimulation (30 Volts) to the right hind limb was applied by pressing a manual switch. The effects of the PMA on EMG were recorded with a bioelectrical amplifier (San-Ei, Japan) on a computer (Data-Q). The amount of IEMG voltage of ten point data moving average were calculated with Math CAD.

Body weight, urination (measuring the frequency of urination during the period of observed locomotor behaviors in mice), death, compulsive motor behavior, and spontaneous motor behavior were determined at lst day, 2nd day, 3rd day, lst week, 2nd week and 3rd week, respectively. Some results are expressed a mean $\pm$ standard error. Data were compared using one-way test analysis of variance (ANOVA) followed by Dunnette's test or Student's t test. Values of $P < 0.05$ were regarded as significant.

Results

Phenylmercury compounds and methoxyalky mercury compounds are among the organic compounds which split rapidly in the body and are of toxicological importance. Acute poisoning of these organic mercury compounds is likely to cause renal failure due to acute necrosis of the glomerular and/or proximal tubular epithelium, anuria and uremia then occur, leading to death.

As shown in Fig. 1, Panel A, both doses of 22.5 mg/kg and 30 mg/kg of PMA decreased urination of mice. PMA at dose of 30 mg/kg acutely decreased the urination of mice to 20 % of pretreatment measurement on the 2nd day. Although the urination of mice returned 69 % of pretreatment measurement at 1st week after PMA treatment, urination never completely recover to pretreatment rates by the end of this study. In addition, PMA caused death (Fig. 1, Panel C) and decreased body weight (Fig. 2) in mice in a dose-dependent manner. In fact, the time of death most often occurred within the 1st week after treatment with PMA, which might have induced acute glomerular injury and acute tubular necrosis in the mice, causing them to die. The decrease in body weight caused by PMA lasted for 3 weeks, and although the body weight of PMA-treated mice gradually increased during the 3-week observation period, it remained much lower than that of control group (Fig. 2). As shown in Fig. 1, Panel B, PMA also decreased the rotarod performance of mice in a dose-dependent manner. However, both the 22.5 mg/kg dose and 30 mg/kg dose of PMA markedly decreased the rotarod performance of mice from the 1st day to 3rd day after PMA treatment. While one recovery in rotarod performance was observed, it never completely recovered by the end of the experiment.

In our study of multivariate locomotor behaviors, which included total distance, move time, vertical time, vertical activity, stereotypy number, stereotypy time, and stereotypy counts, although a dose of 30 mg/kg decreased all the multivariate locomotor behaviors (Fig. 3－Fig. 9) through out the entire experimental time, only the stereotypy behaviors (stereotypy time, stereotypy number and stereotypy counts) were significantly decreased by 30 mg/kg PMA (Fig. 7－Fig. 9). The other dosages (7.5 mg/kg－22.5 mg/kg) of PMA decreased all the multivariate locomotor behaviors initially, but then they were found to increase over time. However, both the attenuated and potentiated effects of PMA on locomotor behavior at these doses (≦ 22.5 mg/kg) did not show any significant difference when compared with those of the control mice at each time of observation.

As shown in Fig. 10, 30 mg/kg of PMA significantly decreased DOPAC concentrations in the limbic area and decreased the potential of IEMG in rectus femoris muscle as compared with those of the controls.

Discussion

Although the use of mercury compounds in agriculture and in industry has been limited through legislation in most countries, occupational and accidental exposure still occurs. Many paint companies have used PMA as a preservative to prolong the shelf life of interior latex paint. Unfortunately, PMA is released in these paints, causing acrodynia in children whose homes were painted with such paints [6]. In this study, PMA was found to decrease the body weight of mice in a dose-dependent manner, a finding observed in rats by other authors [5,17]. Tamborini et al. (1989) reported that PMA caused a decrease in body weight in rats paralleled which a decrease in their daily food consumption [17]. The decrease in body weight of the mice in this study might be due to the same reason. However, with PMA, we observed PMA caused death of mice in a dose-dependent manner, while Tamborini et al. (1989) reported that each rat survived after treatment [17]. The difference in results might be accounted for by the use of different species labortary animals (mice vs. rats) or administrative method (SC vs. oral).

Phenylmercury acetate is the organic compound, which can split rapidly into inorganic mercury [23] in the body, is of toxicological importance. Inorganic mercury has been reported to

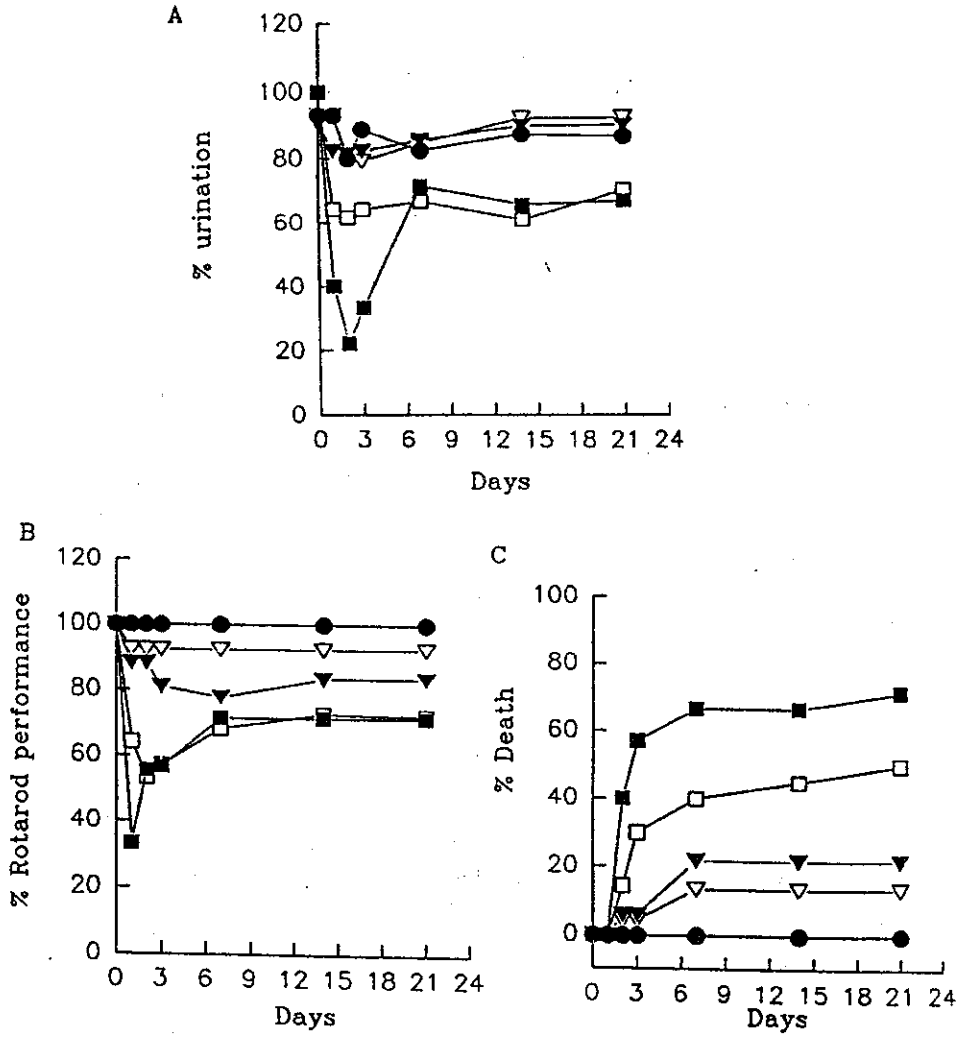

Fig. 1 Effect of phenylmercury acetate (PMA) on rotarod performance, urination and death of mice after subcutaneous administration. Panel A, urination; Panel B, rotarod performance; Panel C, death. ●—●: control; ▽—▽: 7.5 mg/kg PMA; ▼—▼: 15 mg/kg, PMA; □—□: 22.5 mg/kg PMA; ■—■: 30 mg/kg PMA.

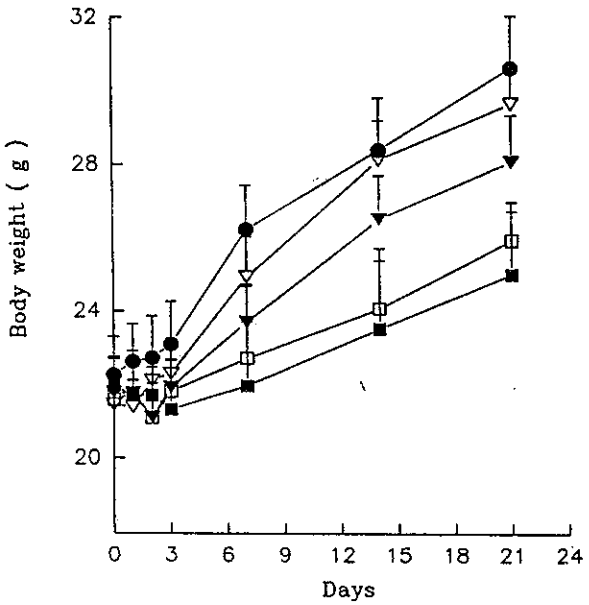

Fig. 2 Effect of phenylmercury acetate (PMA) on body weight of mice after subcutaneous adminstration. ●—●: control; ▽—▽: 7.5 mg/kg PMA; ▼—▼: 15 mg/kg PMA; □—□: 22.5 mg/kg PMA; ■—■: 30 mg/kg PMA. Data are presented as mean ± S.E.

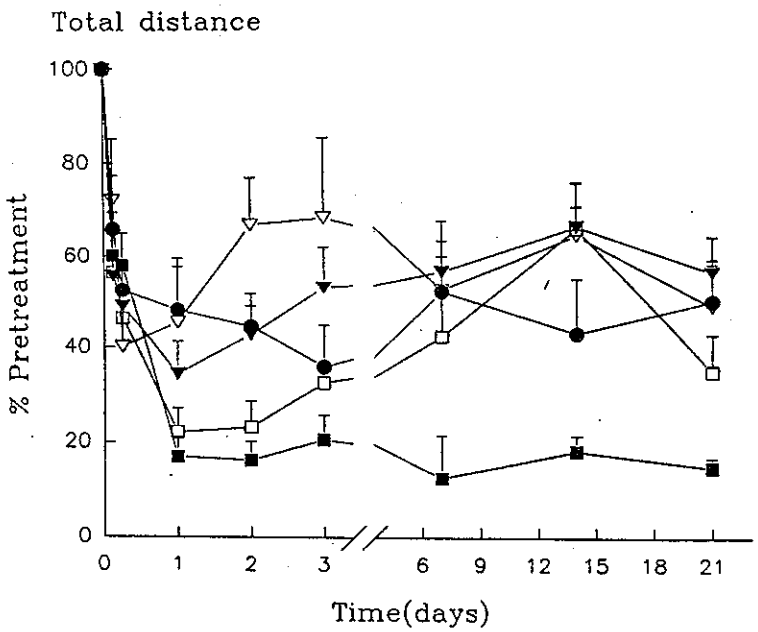

Fig. 3 Effect of phenylmercury acetate (PMA) on total distance of spontaneous movement in mice that was observed by the automated Digiscan Animal Activity Monitor (Omnitech). ●—●: control; ▽—▽: 7.5 mg/kg PMA; ▼—▼: 15 mg/kg PMA; □—□: 22.5 mg/kg PMA; ■—■: 30 mg/kg PMA. Data are presented as mean ± S.E.

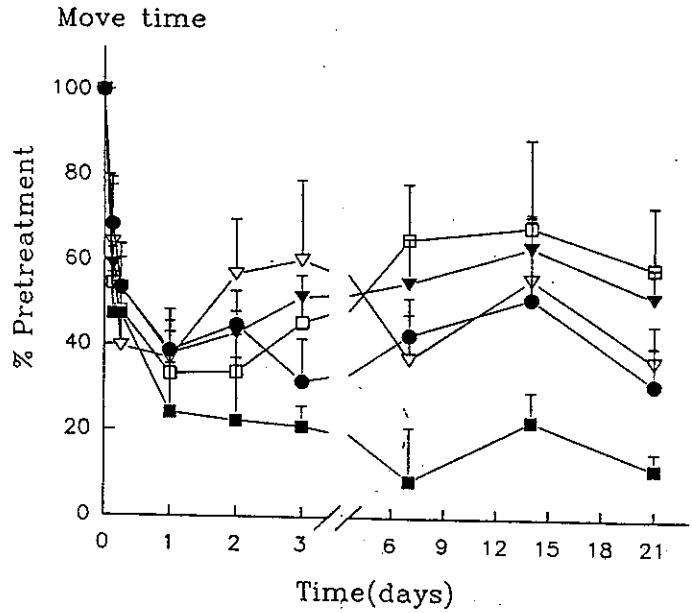

Fig. 4 Effect of phenylmercury acetate (PMA) on movement time of spontaneous movement in mice that was observed by the automated Digiscan Animal Activity Monitor (Omnitech). ●—●: control; ▽—▽: 7.5 mg/kg PMA; ▼—▼: 15 mg/kg PMA; □—□: 22.5 mg/kg PMA; ■—■: 30 mg/kg PMA. Data are presented as mean ± S.E.

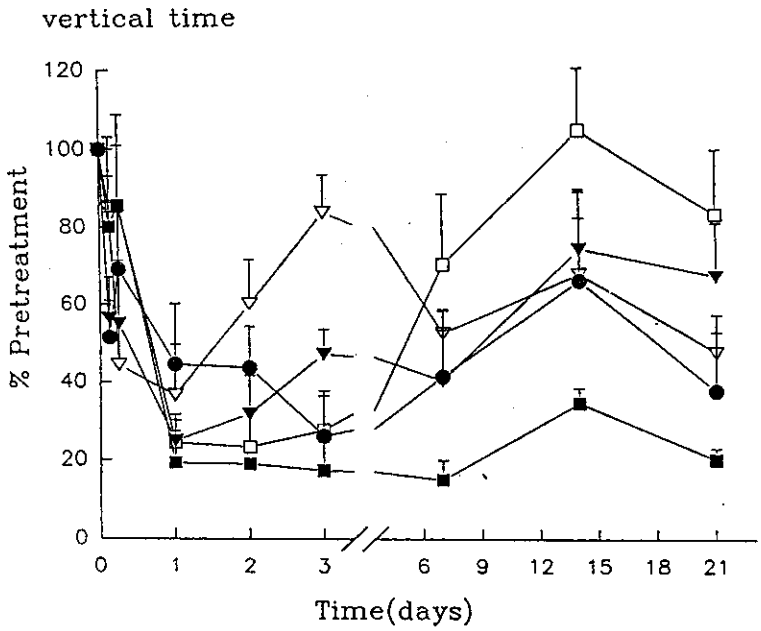

Fig. 5 Effect of phenylmercury acetate (PMA) on vertical time of spontaneous movement in mice that was observed by the automated Digiscan Animal Activity Monitor (Omnitech). ●—●: control; ▽—▽: 7.5 mg/kg PMA; ▼—▼: 15 mg/kg PMA; □—□: 22.5 mg/kg PMA; ■—■: 30 mg/kg PMA. Data are presented as mean ± S.E.

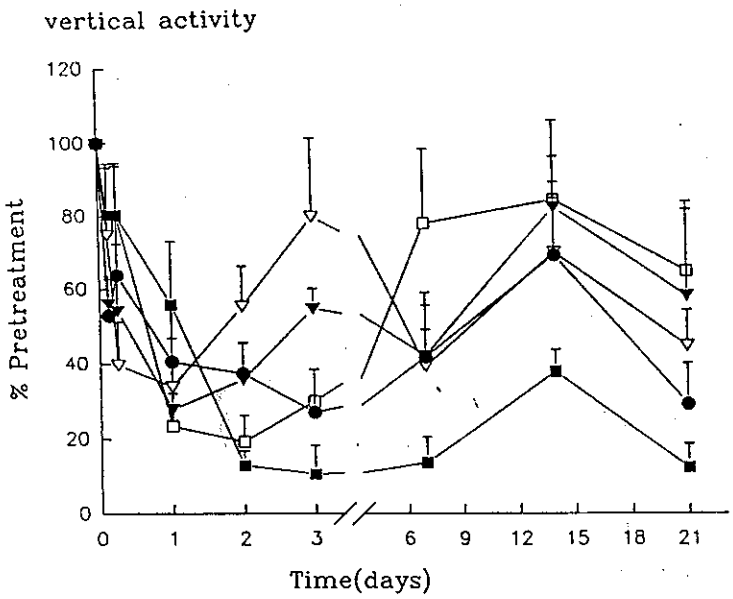

Fig. 6 Effect of phenylmercury acetate (PMA) on vertical activity of spontaneous movement in mice that was observed by the automated Digiscan Animal Activity Monitor (Omnitech). ●−●: control; ▽−▽: 7.5 mg/kg PMA; ▼−▼: 15 mg/kg PMA; □−□: 22.5 mg/kg PMA; ■−■: 30 mg/kg PMA. Data are presented as mean ± S.E.

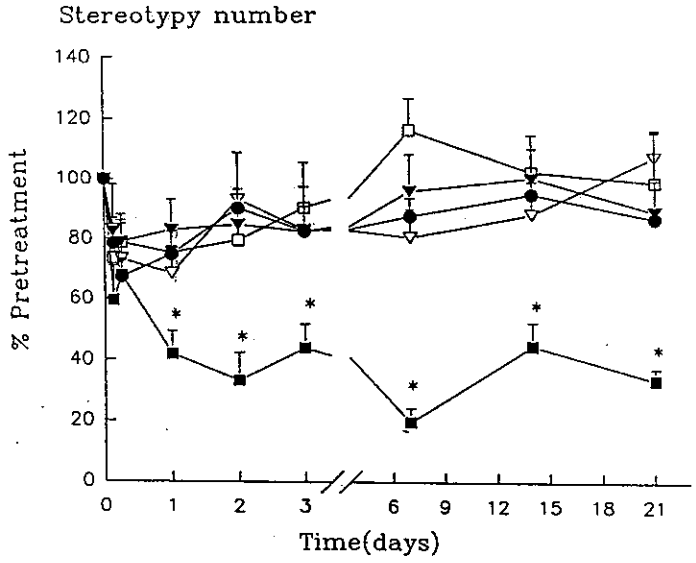

Fig. 7 Effect of phenylmercury acetate (PMA) on stereotypy time of spontaneous movement in mice that was observed by the automated Digiscan Animal Activity Monitor (Omnitech). ●−●: control; ▽−▽: 7.5 mg/kg PMA; ▼−▼: 15 mg/kg PMA; □−□: 22.5 mg/kg PMA; ■−■: 30 mg/kg PMA. Data are presented as mean ± S.E.
*P < 0.05, significantly different from control at each observing time.

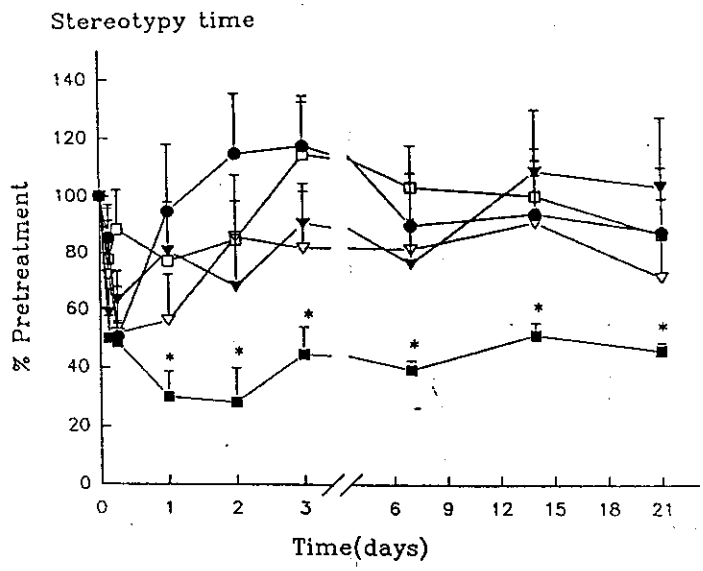

Fig. 8 Effect of phenylmercury acetate (PMA) on stereotypy number of spontaneous movement in mice that was observed by the automated Digiscan Animal Activity Monitor (Omnitech). ●—●: control; ▽—▽: 7.5 mg/kg PMA; ▼—▼: 15 mg/kg PMA; □—□: 22.5 mg/kg PMA; ■—■: 30 mg/kg PMA. Data are presented as mean ± S.E.
*P< 0.05, significantly different from control at each observing time.

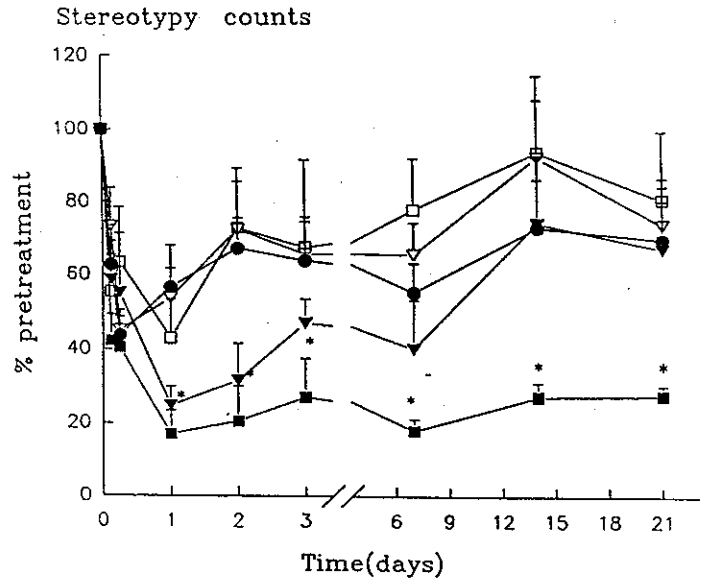

Fig. 9 Effect of phenylmercury acetate (PMA) on stereotypy counts of spontaneous movement in mice that was observed by the automated Digiscan Animal Activity Monitor (Omnitech). ●—●: control; ▽—▽: 7.5 mg/kg PMA; ▼—▼: 15 mg/kg PMA; □—□: 22.5 mg/kg PMA; ■—■: 30 mg/kg PMA. Data are presented as mean ± S.E.
*P < 0.05, significantly different from control at each observing time.

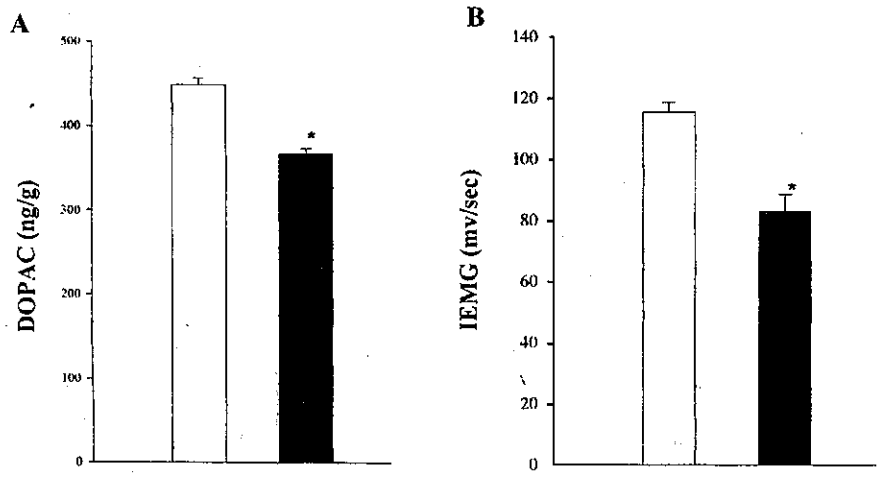

Fig. 10 Effects of phenylmercury acetate (PMA; 30 mg/kg) on DOPAC concentration in limbic area (panel A) and potential of integral electromyograph (IEMG) in rectus femoris muscle (panel B) in mice at first day after PMA treatments. □: control; ■: PMA. Data are presented as mean ± S.E.
*P < 0.05 as compared with control.

accumulate in the kidney and cause glomerular injury and/or tubular necrosis. Such renal dysfunction may have caused the decrease in urination in PMA treated mice in this study. Furthermore, acute metal exposure can induce the synthesis of metallothionien in a number of tissues [24] and a large proportion of mercury in the kidney is bound to metallothionein [25], which can explain the attenuation of PMA-induced renal toxicity the 3rd day after treatment.

Rats that have been given bilateral injections of the cholinergic neurotoxin have shown enhanced stereotypy time [26]. Sanberg et al. (1984) injected rats with 4.0 mg/kg of the dopamine receptor agonist, d-amphetamine, resulting in incremental increases in stereotypy time [27]. Greese and Inversen (1973) also reported that amphetamine enhanced stereotypy time in adult rats [28]. The adult brain and the fetal brain in squirrel monkies show a special affinity for methylmercury, with levels of alkylmercury at least 3-6 times higher in the brain than in the blood, with the accumulation of methylmercury in the brain giving rise to neuronal damage [29]. Hrdina et al. (1976), on the other hand, have reported a decrease in cortical acetylcholine and serotonin in the brain stem of methyl mercury poisoned rats [30]. Verity et al. (1975) demonstrated tnat local injection of methylmercury in the vicinity of the sciatic nerve resulted in total blockage of axon flow [31]. Studies of the electrical organ of the Torpedo oscillata have shown that methylmercury with high specificity blocks the acetylcholine receptors [32]. Since the logarithmic octanol-water partition coefficient (an indicator of lipophilicity) of PMA is higher than that of methylmercury [33], PMA might be like methylmercury affecting neurotransmitter concentrations in the brain and combining with degenerative changes in the central and peripheral nerves [34]. In this study, we found that PMA significantly decreased the concentration of DOPAC in the limbic area and decreased the potential of IEMG. Accordingly, PMA caused a decrease in rotarod performance and in stereotypy behaviors in mice in this study, which may indi-

cate both central and peripheral site involvement, we tentatively assume that the neurotoxin sites of PMA involve at least the mesolimbic dopaminergic pathway and the cholinergic pathway.

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苯基汞影響成熟雄性小白鼠之運動行為及其他生理功能的研究

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在成熟雄性小白鼠單一皮下注射苯基汞（PMA），給予濃度分別是，7.5、15、22.5和30mg/kg，給藥後加以觀察21天。分別在第一天、第二天、第三天、第一週、第二週與第三週探討小白鼠之旋轉運動能力、多項自發性運動行為和生理功能的變化。小白鼠之旋轉運動能力是在旋轉跑步機（Rotarod treadmill）中執行。多項自發性運動行為，則在自發性運動行為記錄儀（Digiscan system）中進行。PMA只在30mg/kg劑量下，才具統計意義的降低小白鼠之重複性行為（重複性行為時間、重複性行為數目、重複性行為次數）。在給予PMA 22.5mg／kg與30mg／kg後的第一、二、三天，二種劑量皆顯著的降低小白鼠旋轉運動能力的表現及排尿量。此外，PMA劑量-相關性地降低小白鼠之體重和造成死亡。既然PMA可降低小白鼠腦邊緣區之DOPAC濃度和股直肌之肌電位，所以PMA降低小白鼠之重複性行為和旋轉運動能力的毒性，包括作用到中樞神經以及末稍神經，而且我們推測PMA的傷害神經區域，至少包括了中腦－腦邊緣系多巴胺系路徑以及膽鹼激素系路徑。

關鍵詞：苯基汞、運動行為、成熟雄鼠

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