定结构和活性比较的结果以及分子动力学的关系式计算了45个ZNC(C)PR类似物的能量和可能的结构趋向，从理论上探讨了各残基对稳定结构的贡献，并据此设计和合成了5个新的类似物加以验证．结果与预测相符．即一定紧密度的分子结构是表现活性所必需的．

关键词 学习；记忆；神经肽；结构-活性关系

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Effects of low level lead exposure on behavior of young rats[1]

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ABSTRACT Dam rats were given Pb (0.58, 1.76, and 5.27 $mmol \cdot L^{-1}$), containing water *ad lib* from d 16 of gestation to weaning of the offspring on d 21 postpartum. The pups continued drinking the same water till the postnatal d 30. The neurobehavioral function of pups was tested. The second step-down latencies (SDL_2) were shortened and the number of step-downs in 5 min (NSD) were increased in step-down test. The prolongation of the lapse of time in passing through the whole course (LTPWC) and the increase in number of entries into the blind alley (NEBA) were measured in water maze test. The number of ambulations and rearings were increased in locomotor activity. The results indicated that Pb exerts adverse effects on the learning ability and memory function, and induces hyperactivity in young rats.

KEY WORDS lead poisoning; animal behavior; learning disorders; memory disorders; locomotion

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Pb-induced neurobehavioral effects were reported both in children and rats[1-3]. However, relatively few studies on behavioral status of young rats exposed to low level Pb had been reported. The present study described the findings of neurobehavioral effects in terms of cognition, spontaneous activity, and muscle-coordination due to low level Pb exposure.

MATERIALS AND METHODS

Rats Sprague-Dawley rats (♀, $n=21$) on d 16 of pregnancy (weighing 352 ± 28 g) were randomly divided into 3 Pb-poisoned groups and a control group. The poisoned groups were dosed with a solution containing lead acetate (from Shanghai Fourth Chemical Reagent Factory) 5.27, 1.76, and 0.58 $mmol \cdot L^{-1}$, respectively, in drinking water and the control group was given distilled water from d 16 of gestation to weaning of the offspring on d 21 postpartum. The pups continued drinking the same water till postnatal d 30. On postnatal d 30, 6 ♂ and 6 ♀ pups per group were used for neurobehavioral tests.

Lead assay The rats were decapitated. Pb contents in blood and cortices were determined using a Hitachi-80 flameless atomic absorption spectrophotometer.

Neurobehavioral tests

1 Water maze A water maze[4] of 100 cm × 50 cm × 35 cm was used. LTPWC and NEBA were recorded.

2 Step-down Each rat was placed gently on a wooden platform 4 cm×4 cm in size, and 5 cm high. The first step-down latency (SDL_1) was measured, when the rat stepped down from the platform and placed all its 4 paws on the grid floor. A sustained electric stimulation (ES, 0.4—0.5 mA) from an electric stimulator (provided by Shanghai Institute of Physiology, Chinese Academy of Sciences) was delivered till the rat returned to the platform for escaping from the ES. The escape latency (EL), SDL_2, and NSD were also measured[4].

3 Locomotor activity Ambulation was measured by counting the times of crossing over the middle of the floor and rearing was recorded by counting the times the rat stood on its hindlegs with its forelegs against the cage wall. The preening behavior and the number of blouses deposited were recorded[5].

4 Rotarod Each rat was placed on a cylinder of a rotarod treadmill rotating at a speed of 9 or 18 rotations·min^{-1} (RPM). When the rat fell off from the cylinder onto the plate below, the endurance time of the rat was recorded[6].

Statistical analyses dBASE III was served as database, and ANOVA were conducted with SPSS/PC + software on IBM personal computer

RESULTS

Maternal and preweaning toxicity Exposure to lead acetate had no significant effect on weight gain of the dams during gestation and lactation. However, the average number of pups per litter in 0.58, 1.76, 5.27 mmol·L^{-1} Pb-poisoned groups and the control group were 9.8±1.9, 11.2±1.3, 9.0±2.0, and 12.0±2.7, respectively, indicating a decrease in 5.27 mmol·L^{-1} Pb-poisoned group *vs* control ($P<0.05$). Body weight of the pups on postnatal d 21 and d 30 did not show significant differences between Pb-poisoned and the control groups.

Pb concentrations in blood and brain Administration of Pb produced increases in blood and cortical Pb level (Tab 1).

Water maze LTPWC was prolonged in 1.76 and 5.27 mmol·L^{-1} ♂ and ♀ groups and NEBA was also increased in 3 ♂ groups and in 1.76, and 5.27 mmol·L^{-1} ♀ groups (Tab 1).

Step-down SDL_2 were shortened and NSD were increased in all the 3 Pb-poisoned groups (Tab 1).

Locomotor activity The Pb-poisoned rats showed increased ambulatory and rearing behavior *vs* controls. The times of preening were decreased in all Pb-poisoned groups (Tab 1).

Effects on rotarod performance At treadmill speeds of 9 and 18 RPM, the rotarod performance revealed no deficit in the motor coordination of the Pb-poisoned rats.

DISCUSSION

Since the influence of Pb to the nervous system was most obvious in developing period in human and rat[7], Pb was administered from gestation d 16 to postnatal d 30. Brain cortex had higher Pb concentrations than other brain areas in Pb-exposed rats[8-9], therefore, Pb contents in brain cortex was used as the representation of brain Pb. The Pb concentrations in blood and brain cortex of ♂ and ♀ rat increased correspondingly as the amount of Pb administered to rats increased. Thus indicated that Pb was successfully assimilated by rats.

The present study showed that there were no effects of Pb on the body weight of dams and pups and thus excluded the possible influence on behavior of pups induced by malnutrition. But a decrease in number of pups per litter in 5.27 mmol·L^{-1} Pb-poisoned group indicated genital toxicity induced by Pb.

Performance of rats in water maze, step-down, locomotor activity and rotarod could show their learning ability, memory function,

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Tab 1. Pb concentrations in blood (μmol·L^{-1}) and brain cortex (mg/g dry tissue) of dam and pup rats and differences in lapse of time in passing through the whole course (LTPWC), number of entries into blind alley (NEBA), first step-down latency (SDL$_1$), escape latency (EL), second step-down latency (SDL$_2$), number of step-down in 5 min (NSD), ambulation, rearing, preening, and defecation in pup rats exposed to Pb by drinking water *ad lib* from d 16 of gestation to postnatal d 30. $n=6$, $\bar{x}\pm s$. [a]$P>0.05$, [b]$P<0.05$, [c]$P<0.01$ *vs* control.

Rats	Parameter	mmol Pb/liter of drinking water 0	0.58	1.76	5.27
♂ pups	Blood Pb	0.09±0.07	0.83±0.15[c]	1.33±0.16[c]	3.08±0.10[c]
	Cortex Pb	0.4±0.2	0.7±0.3[a]	1.2±0.2[c]	2.0±0.5[c]
♀ pups	Blood Pb	0.07±0.05	0.70±0.10[c]	1.28±0.27[c]	2.75±0.69[c]
	Cortex Pb	0.3±0.2	0.6±0.1[a]	0.8±0.1[c]	2.0±0.6[c]
Dams	Blood Pb	0.45±0.15	1.93±0.35[c]	2.50±0.57[c]	3.26±1.11[c]
♂ pups	LTPWC	19.0±5.2	59.7±24.2[a]	95.3±59.0[c]	117.2±29.6
	NEBA	1.3±0.8	5.5±2.3[b]	8.2±4.0[c]	10.5±2.3[c]
♀ pups	LTPWC	29.2±16.9	33.3±18.7[a]	84.2±42.0[b]	115.5±14.0[b]
	NEBA	2.8±2.5	3.2±2.6[a]	8.2±4.0[c]	9.3±1.2[c]
♂ pups	SDL$_1$	2.3±1.0	2.0±2.4[a]	3.5±3.0[a]	2.5±3.6[a]
	EL	57.3±51.4	72.0±43.3[a]	71.8±42.6[c]	89.2±13.2[a]
	SDL$_2$	215.0±133.5	40.3±41.9[c]	35.2±44.5[c]	24.5±19.7[c]
	NSD	1.3±0.5	3.3±1.4[c]	4.2±1.3[c]	6.0±1.3[c]
♀ pups	SDL$_1$	9.1±16.9	8.8±11.4[a]	2.7±3.6[c]	11.5±13.8[a]
	EL	58.6±39.7	63.2±47.9[a]	89.0±49.2[a]	90.3±48.5[c]
	SDL$_2$	142.3±135.4	24.0±26.8[c]	33.7±38.5[c]	8.0±8.4[c]
	NSD	1.9±1.0	3.2±0.8[b]	3.3±1.2[b]	3.8±1.5[c]
♂ pups	Ambulation	16.5±4.5	17.3±5.1[a]	18.5±3.8[a]	24.0±2.8[c]
	Rearing	11.8±2.9	14.5±4.4[a]	18.0±2.2[b]	20.0±5.2[c]
	Preening	2.2±1.3	2.3±1.0[a]	1.8±1.2[a]	1.7±1.4[a]
	Defecation	0.7±1.6	1.0±1.5[a]	0.8±2.0[a]	0.8±1.3[a]
♀ pups	Ambulation	16.0±5.1	18.8±4.2[a]	17.8±5.6[a]	24.2±3.3[b]
	Rearing	13.2±6.6	14.8±5.3[a]	17.8±4.4[a]	24.2±4.8[a]
	Preening	3.2±1.6	2.7±1.5[a]	2.2±1.0[a]	1.2±0.8[b]
	Defecation	0.2±0.4	0.0±0.0[a]	0.0±0.0[a]	0.8±2.0[a]

exploratory activity, adaptability to novel situation[3-6] and muscle coordination. The behavioral impairment in the present study was similar to those previously reported[8-9]. It demonstrated that low level Pb exposure to young rats can apparently decrease the learning ability and memory function, increase the exploratory activity, and decrease the adaptability to novel situtation. Disturbed rotarod performance reported by Kishi and Uchino[9] was not observed in present study. The discrepancy of the results may be attributed to the higher blood Pb concentrations (1.86 ± s 1.08 mg·L^{-1}) in their study.

It should be emphasized that behavioral abnormality was found in 0.58 mmol·L^{-1} group even though Pb content in brain cortex of this group did not increase *vs* control. The reason for this lies in that Pb-induced neurotoxicity includes a series of toxicological events and the damage to only a small number of localized neurons can lead to a profound consequences for the overall performance of the organism.

In summary, low level Pb exposure can exerts adverse effects on learning ability and memory function, and induces hyperactivity.

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低剂量铅接触对幼大鼠行为的影响

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摘要 SD 雌大鼠从妊娠 d 16到分娩后 d 21摄取含铅水，断奶后仔鼠仍摄取至出生后 d 30. 测试仔鼠行为. 步下法中，第二次下台潜伏期缩短，5 min 内的下台次数增加；水迷宫测试中，通过水迷宫的时间延长，进入盲端的次数增加；且自发活动增强，对新环境的适应性下降. 结果表明低剂量铅使幼鼠学习和记忆能力下降，活动增加.

关键词 铅中毒；动物行为；学习障碍；记忆障碍；行动

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