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应用小鼠在Y形迷宫中的自主选择能力测定急性及慢性东莨菪碱与吗啡对记忆的影响

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摘 要 应用Y型迷宫研究了急性与慢性东莨菪碱和吗啡对小鼠记忆能力的影响. 单剂量东莨菪碱(1 mg/kg ip)和吗啡(10 mg/kg ip)均能显著损害小鼠的短时记忆(working memory)。重复给药后东莨菪碱的这种作用很快消失。但吗啡每天一次，连续3次给药这种作用加强，连续5次给药这种作用反而减弱。东莨菪碱不能损害小鼠长时记忆(reference memory)，而吗啡对长时记忆有损害作用。结果还提示小鼠短时记忆不受自发活动能力的影响。

关键词 东莨菪碱；吗啡；记忆；自主选择能力；活动能力

Effects of Acute and Chronic Scopolamine and Morphine on Memory in Mice Using a Y-maze Spontaneous Alternation Task

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Abstract The acute and chronic effects of scopolamine and morphine on memory were assesed using a Y-maze spontaneous alternation task in mice. Single dose of scopolamine (1 mg/kg ip) or morphine(10 mg/kg ip) significantly impaired working memory. With repeated doses, this effect of scopolamine diminished very rapidly. However, following 3 doses of morphine, this effect was enhanced, after 5 repeated doses, it did not exert significant effects. Scopolamine did not disrupt reference memory, while morphine produced reference memory impairment. Experimental data also suggested that spontaneous alternation performance and locomotor activity were independent behaviors.

Key words Scopolamine; Morphine; Memory; Spontaneous alternation perfoomance; locomotor activity

In 1988, Sarter[1] proposed that spontaneous alternation performance in a Y-maze, which required an ability to remember prior selections, could reflect working memory, which referred to the recall of recent events of transient importance. Since then, the Y-maze spontaneous alternation task has been extensively employed in the study of working memory. Here we use the Y-maze spontaneous alternation task to examine the effects of acute and chronic scopolamine and morphine treatment on memory.

It is well known that cholinergic system plays a pivotal role in regulating memory processes. Many investigations have shown that single injection of the anticholinergic drug, scopolamine, produces an especially disruptive effect on memory[2]. A recent finding showed that chronic administration of scopolamine also impairs memory measured both during and after training in a water maze task[3]. However, another study demonstrated that tolerence to the memory-impairing effect of scopolamine can occur after repeated administration in a delayed-nonmatching-to-sample task[4]. Further, with a single trial passive avoidance task, Loullis and his colleagues found that if continuous infusion of scopolamine to rats through subcutaneously implanted pumps for 15 d, the retention that was tested 48 h after drug elimination is enhanced[5]. The completely different effects of chronic scopolamine on memory might be due to the different tasks employed in respective study. In the Y-maze spontaneous alternation task, considerable evidence indicated that single injection of scopolamine impairs spontaneous alternation performance[1,6~12]. However, to our knowledge the effect of chronic scopolamine on spontaneous alternation performance has not been reported.

Besides cholinergic agents, opioids also play an important role in memory processes[13]. Our previous work demonstrated that morphine, produces bi-directional effect in memory processes, single pre-training administration induces amnesic state and pre-test treatment facilitates memory retrieval in a one trial passive avoidance task, and both effects are mediated through opioid μ receptors[14]. There are also controversies

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surrounding chronic morphine affecting memory processes. Sala reported that repeated adminstration of morphine produces a residual working memory impairment when the rats were tested 6 and 9 month later in a radial maze task[15]. However, other investigators[16] have shown that 6 weeks of morphine exposure does not impair working memory of rats in a radial maze task, although the reference memory was impaired both in the radial maze task and in a Y-maze choice escape task. Another group of authors reported that a daily repeated ip injection of morphine slows acquisition and impairs cue learning but does not impair retention in a water maze task[17]. In the Y-maze spontaneous alternation task nobody has examined the chronic morphine effect on spontaneous alternation performance, although acute morphine effect has been investigated[8,9,18]. The main purpose of the present study is to compare the effects of acute treatments of scopolamine and morphine with the effects of their more or less prolonged administration on memory respectively, in a Y-maze spoataneous alternation task, and to compare the characterization of the amnesic effects of scopolamine and morphine. In addition, since the spontaneous alternation performance might be influenced by locomotor activity, the relation between spontaneous alternation performance and locomotor activity was discussed.

1 Materials and methods

1.1 *Animals*

Male mice of the ddY strain (Ohtsubo EXP. Animals, Nagasaki), weighing 18-20 g, were housed in plastic cages with free access to food and water. They were kept in a temperature-controlled room at 22±1 C under a natural day/night regime. After reaching 25-30 g, they were used for the experiments. Behavioral testing was performed between 10:00 a.m. and 3:00 p.m.

1.2 *Drugs*

Morphine-HCL (Takeda, Osaka), scopolamine-HCL(Tokyo Kasei, Tokyo). Both drugs were dissolved in saline and were administered ip in a volume of 0.1 ml/10 g body weight. Control group received saline in the same volume. Doses are expressed in terms of the salts.

1.3 *Apparatus*

Spontaneous alternation behavior was assessed in a Y-maze. The center of the maze is shaped as hexagon and served as the start position.

1.4 *Procedures*

Experiments were designed in 2 schedules: Schedule 1, daily injection daily test, scopolamine (1 mg/kg) or morphine (10 mg/kg) was daily administered ip 30 min before each trial for 5 d; Schedule 2, different duration of drug exposure single test, scopolamine (1 mg/kg) or morphine (10 mg/kg) was daily administered ip for 1, 3 or 5 d, 30 min after the final injection tests were conducted on the test days respectively. The testing procedure was based on that of Sarter[1]. Following drug treatment, each mouse was placed at the center of the maze and allowed to move freely through the maze for an 8-min test session while the sequence of arms entered by the subject was recorded manually. An arm entry was defined as the body of the mouse except for its tail completely entering into an arm. An alternation was defined as the entry into all three arms on consecutive choices. The number of possible alternations was then the total number of arms entered minus 2, and the percent alternation was calculated as (actual alternations/possible alternations) × 100. For example, if the 3 arms were called A, B, and C, and a mouse entered arms ACBBAC, there would be 2 alternations out of 4(6-2) possible, resulting in a percent alternation score of 50. Mice that entered arms less than 8 times during the test were eliminated, because the data obtained from those mice were not considered to reflect precise alternation.

1.5 *Statistical analysis*

All results were expressed as the means ± S.E. and analyzed by Student's *t*-test. The difference was considered to be significant at $P < 0.05$.

2 Results

2.1 *Effects of scopolamine on spontaneous alternation performance and total arm entries*

In the schedule 1 tests, on d 1, the percent alternation of scopolamine-treated mice significantly decreased compared with that of saline-treated mice, but from d 2 to d 5, two groups showed no significant difference; the total arm entries of both scopolamine- and saline-treated mice showed daily decreasing manners through the 5 test days, but on the respective day, the total arm entries of scopolamine-treated mice increased significantly compared with that of saline-treated mice (Fig 1). In the schedule 2 tests, compared with the saline-treated mice, the single dose of scopolamine-treated mice, percent alternation decreased significantly ($P<0.01$), total arm entries increased significantly ($P<0.05$); the 3 doses treated mice, percent alternation tended to decrease, total arm entries tended to increase, but not markedly; the 5 doses treated mice, percent alternation showed no significant change, total arm entries showed a increase tendency but did not prove to be statistically significant (Fig 2).

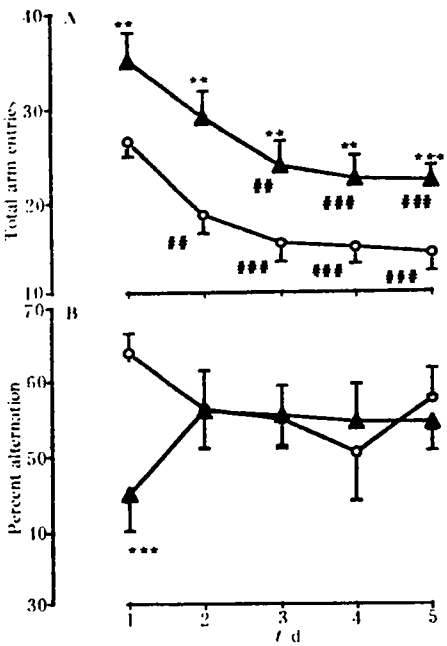

Fig 1. Effects of 5 daily scopolamine treatments on the total arm entries (A) and spontaneous alternation (B) in the Y-maze. Scopolamine (▲) 1.0 mg/kg was daily administered ip 30 min before each trial for 5 days ($n=10$). Control group ($n=10$) received saline (○) instead of scopolamine. Data are expressed as the mean ± S.E. (vertical bars). $^{**}P<0.05$, $^{***}P<0.01$ vs. control on the corresponding day. $^{\#\#}P<0.05$, $^{\#\#\#}P<0.01$ vs. the 1st trial result in the respective group.

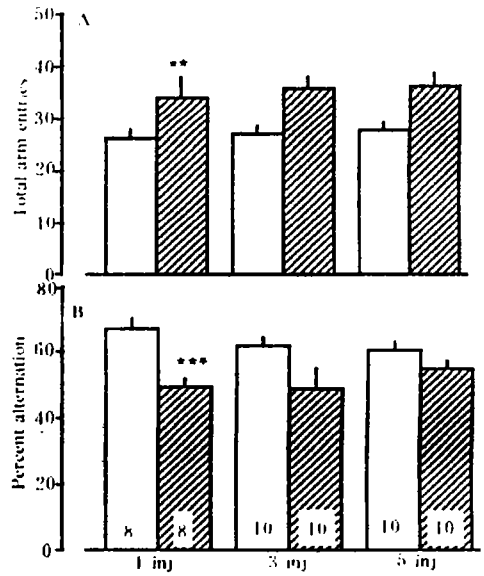

Fig 2. Effects of single or repeated treatments of scopolamine on the total arm entries (A) and spontaneous alternation (B) in the Y-maze. Scopolamine (1 mg/kg) was daily administered for 1, 3 and 5 d respectively. Control groups received saline (□) instead of scopolamine (▨). The tests were performed 30 min after the final injection (inj) on the test days. Data are expressed as the mean ± S.E. (vertical bars). The number of mice used is shown in the column. $^{**}P<0.05$, $^{***}P<0.01$ vs. control.

2.2 *Effects of morphine on spontaneous alternation performance and total arm entries*

In the mice treated daily with 10 mg/kg of ip morphine 30 min prior to each trial for 5 d, from d 1 to d 3, the percent alternation revealed a significant reduction in a daily enhancing manner compared with that in saline-treated mice, however, from d 4 on the impairing effect decreased, on d 5 two groups appeared no significant difference (Fig 3 B); Fig. 3 A illustrated the effect of morphine on total arm entries, in the saline-treated mice, the total arm entries decreased day by day, while the total arm entries of morphine-treated mice did not change through the 5 d, thus, on every test day morphine group showed a significant increase compared with control group. In the schedule 2 tests, compared

with saline- treated mice, single dose of morphine- treated mice, percent alternation significantly decreased ($P<0.05$), total arm entries significantly increased ($P<0.01$); the 3 doses treated mice, percent alternation decreased drastically ($P<0.01$), whereas total arm entries showed no marked change; the 5 doses treated mice, both percent alternation and total arm entries did not reveal significant change(Fig 1).

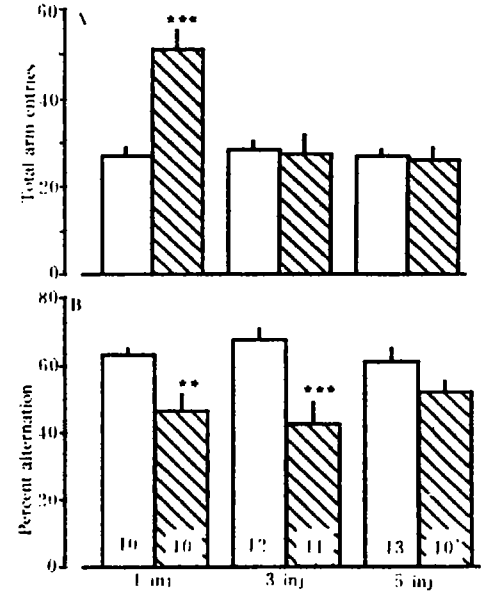

Fig 1. Effects of single or repeated treatments of morphine on the total arm entries(A) and spontaneous alternation (B) in the Y- maze. Morphine(10 mg/kg) was daily administered for 1,3 and 5 d respectively. Control groups received saline (□) instead of morphine (▨). The tests were performed 30 min after the final injection (inj) on the test days. Data are expressed as the mean ± S. E. (vertical bars). The number of mice used is shown in the column. $^{**}P<0.05$, $^{***}P<0.01$ vs. control.

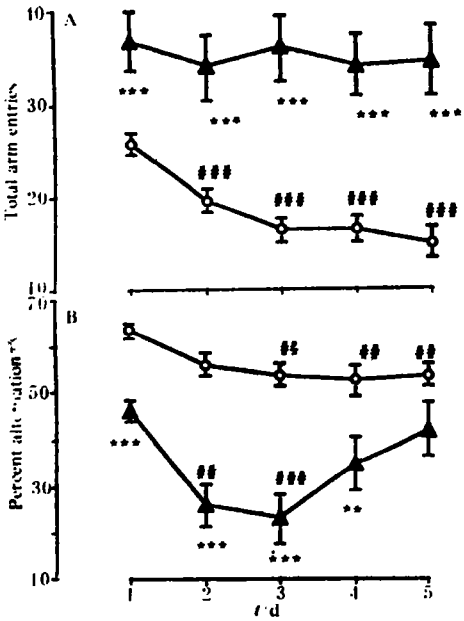

Fig 3. Effects of 5 daily morphine treatments on the total arm entries (A) and spontaneous alternation (B) in the Y- maze. Morphine (▲) 10 mg/kg was daily administered ip 30 min before each trial for 5 d($n=19$). Control group ($n=21$) received saline (○) instead of morphine. Data are expressed as the mean ± S. E. (vertical bars). $^{**}P<0.05$, $^{***}P<0.01$ vs. control on the corresponding day. $^{**}P<0.05$, $^{***}P<0.01$ vs. the 1 st trial result in the respective group.

3 Discussion

The present result showing that single dose of scopolamine impairs spontaneous alternation performance, is consistent with past evidence that cholinergic antagonists impair memory for a broad range of tasks[19]. However, with repeated doses, the spontaneous alternation performance impairing effect of scopolamine diminished very rapidly (Fig 1 B, 2 B). This phenomenon may parsimoniously account for the increase that others have reported in muscarinic receptor sensitivity following chronic cholinergic stimulation[20~22]. According to these findings, repeated doses of scopolamine induce an increase in muscarinic receptor sensitivity, then the effect of endogenous acetylcholine would be potentiated, and hence, an attenuation of scopolamine-induced deficit of spontaneous alternation performance is expected, as we observed here, The result is similar to that of the report of Messer[4] that working memory is impaired and tolerance to the drug scopolamine can occur after intracerebral injections into hippocampus with a delayed-nonmatching-to-sample task, but different from the results of Smith that repeated doses of scopolamine inhibit memory[3], and Loullis that long time continuous infusion of scopolamine improves memory[5]. The different results are possibly due to, as mentioned in the introduction, the different tasks and procedures employed in respective study.

Single dose of morphine, like scopolamine, also impaired spontaneous alternation performance. This result confirmed the reports of Stone[9] and Walker [8]. Further, after 3 daily treatments the impairing effect was enhanced. Following 5 daily treatments, on the contrary, the impairing effect disappeared, suggesting that the effect of morphine on spontaneous alternation performance is drug exposure duration dependent, while daily test or no daily test did not influence the change trend (i. e. the effect is independent of test conditions), because with both schedules we got similar results (Fig 4 B, 5 B). This result might (but not sure in part, due to different duration of chronic opioid agonists exposure) produce different (up-or down-)μ receptor regulation[23]. Three doses of morphine may, in some way, induce μ receptor upregulation. Previous reports that chronic opioid agonists administration alter the release of endogenous anti-opioids such as phe-met-arg- phe- NH_2- like peptides[24,25] resulting in a compensatory upregulation of opiate receptors[26] may support this hypothesis. In fact, Yoburn has already demonstrated that morphine pellets implanted sc for 3 d significantly increased μ receptor density in the whole brain of mice[27]. Another past study revealing the 4 d of postnatal morphine administration produces a complete abolition of [3H]DAMGO binding to μ receptors in striatal patches[28] may help us to understand the phenomenon that following 4-5 daily morphine administrations, the morphine- induced impairment of spontaneous alternation performance precipitously diminished. In addition, following chronic exposure to opioids, the adaptations in G proteins and the cyclic AMP second messenger and protein phosphorylation system have been shown to play an important role in mediating opioid tolerance[29]. This may also help us to understand the diminution of the amnesic effect of morphine after 4～5 d exposure. The report of Spain and Newsom that chronic morphine does not impair working memory in a radial maze task is consistent with present finding[6]. In contrast to our result, Sala reported that chronic morphine produces a residual working memory impairment in rats[15]. The conflicting result may due to the use of different experimental schedule (gradually increasing dosage, and different time of evaluation), task (radial maze task) and subjects (rats).

In the present study, we monitored total arm entries to assess the effects of drugs on locomotor activity. When tested repeatedly with a 1 d interval for 5 d, saline-treated mice showed a daily decreasing total number of arm entries (Fig 1 A, 3 A). This phenomenon may be due to the fact that the mouse learned that there was nothing special in every arm of the maze on the previous day, thus on the following day it did not move as actively as on the previous day. Accordingly, in the schedule 1 tests the total arm entries could be used to assess reference memory (information stored over the long term). In the schedule 1 tests, the total arm entries of morphine- treated mice kept almost the same level through the 5 d (Fig 3 A), indicating that morphine impaired reference memory. This is in accordance with a previous study[16] that chronic morphine treatment impairs reference memory in Y-maze choice escape task and radial maze task. But there is a discrepancy between our result and a past finding that chronic morphine does not impair retention[17]. This difference may account for the different task (water maze) and animal (rats) used in their study. In contrast to morphine effect, scopolamine did not disrupt reference memory because the total arm entries of scopolamine-treated mice, just like saline-treated mice, reduced day by day during the 5 test days (Fig 1 A). This finding is in accordance with previous reports that scopolamine does not significantly influence reference memory in a T-maze special discrimination task[30] and a radial maze task[31].

There are many experiments evaluating interactions between opioids and muscarinic cholinergic system in influencing memory. For example, naloxone reverses scopolamine-induced amnesia of passive avoidance[32] and of spontaneous alternation[8]. Physostigmine blocks amnesia pro-

duced by DAMGO[12] and oxotremorine antagonizes the amnesic effect of β-endorphine[33]. Atropine blocks naloxone enhancement of memory[34]. Based on these findings, it could be speculated that morphine, an opioid agonist and scopolamine, a cholinergic antagonist, produces similar amnesic effects. Our findings that both scopolamine and morphine with single dose impaired working memory in a similar manner support this view. However, we would argue that scopolamine and morphine affect memory not in completely the same manner, since our experimental data showed that with repeated doses, morphine impaired reference memory, while scopolamine did not influence reference memory. Additionally, with 3 doses, morphine- induced working memory deficit was enhanced, but the working memory impairing effect of scopolamine completely disappeared. Thereby we could say that the amnesic effects of scopolamine and morphine are subserved by some common and some different mechanisms.

The present results showed that, with a single dose, both scopolamine and morphine decreased percent alternation and increased total arm entries simaltaneously. Is the decrease of percent alternation due to the increase of total arm entries? Some investigations sought to answer this question have been conducted. With different strains of mice and different tasks, Anisman demonstrated that spontaneous alternation performance and locomotor activity are two dissociative behaviors[7]. Itoh reported that methamphetamine produces great increase in total arm entries but does not prove to influence percent alternation in mice[12]. Their findings support Anisman's conclusion. The present results showing that the daily arm entries kept almost the same level but the percent alternation of respective day was different when morphine was daily administered for 5 d also support the view that spontaneous alternation performance is independent of locomotor activity.

The present findings implied that, 1) the effects of acute and chronic scopolamine or morphine on working memory are different, 2) the memory- impairing effects of scopolamine and morphine possess similarity and discrepancy. And the results supported the view that spontaneous alternation performance and locomotor activity are 2 dissociative behaviors.

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应用小鼠在Y形迷宫中的自主选择能力测定急性及慢性东莨菪碱与吗啡对记忆的影响

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摘 要 应用Y型迷宫研究了急性与慢性东莨菪碱和吗啡对小鼠记忆能力的影响. 单剂量东莨菪碱(1 mg/kg ip)和吗啡(10 mg/kg ip)均能显著损害小鼠的短时记忆(working memory)。重复给药后东莨菪碱的这种作用很快消失。但吗啡每天一次，连续3次给药这种作用加强，连续5次给药这种作用反而减弱。东莨菪碱不能损害小鼠长时记忆(reference memory)，而吗啡对长时记忆有损害作用。结果还提示小鼠短时记忆不受自发活动能力的影响。

关键词 东莨菪碱；吗啡；记忆；自主选择能力；活动能力