Induction of Tolerance to the Ambulation-increasing Effect of Scopolamine in Mice: Importance of the Free Movement in the Early Post-scopolamine Period

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Abstract: Scopolamine (SCP: 0.5, 2 and 8 mg/kg s.c.), a muscarinic anti-cholinergic drug, dose-dependently increased the ambulatory activity of mice for 90 min with the peak effect around 10-20 min after the administration. A significant tolerance to the ambulation-increasing effect of SCP was produced when the mice were repeatedly administered SCP at intervals of 3 days, and they were put into the activity cages of 20 cm in diameter for 90 min after each administration. The mice allowed free ambulation in the activity cages during post-SCP period of 10-60 min, particularly 10-30 min, showed a tolerance to SCP. However, no significant tolerance or sensitization was produced when the ambulation of mice was allowed during the post-SCP period of 0-10min or 60-90 min. The repeated saline-treatment with free or restricted movement produced no significant change in the sensitivity to SCP. The present results suggest that the repeated experience of both the muscarinic anti-cholinergic effect of SCP and the free ambulation during the early post-SCP period of 10-30 min is the essential factor for the induction of tolerance to the ambulation-increasing effect of SCP in mice. Such development of the behavioral tolerance to SCP may be due to the psychopharmacological characteristics of SCP that the harmful symptoms such as dry mouth and eyes produced by blockade of parasympathomimetic nervous systems overwhelm the reward effect (dependence liability) of this drug.
(Reprint request should be sent to Hisashi Kuribara)

Key words: Scopolamine, Behavioral tolerance, Post-scopolamine period, Conditioning, Harmful effect, Mice

Introduction

Scopolamine (SCP) has an antagonistic action on muscarinic acetylcholine receptors, and blocks the parasympathomimetic nervous system. It has been considered that central dopaminergic system (Fink and Morgenstern, 1980) and cholinergic systems (Mathura et al., 1997; Shannon and Peters, 2001; Chintoh et al., 2003) are involved in the SCP-induced hyperactivity. Furthermore, SCP is self-administered by animals (Glick and Goido, 1982; Rasmussen and Fink-Jensen, 2000), and a short-term recreational use of SCP (Brunton et al., 2008) and Angel' s trumpet (Greene et al., 1996) which is a plant containing muscarinic anti-choinergic drugs such as SCP and atropine has been reported, indicating dependence liability of SCP.

Mesolimbic dopaminergic systems (Van der Heuval and Pasterkamp, 2008) play important roles in the behavioral and psychological activities, including motivation (Matsumoto and Hikosaka, 2009), learning and memory (Arias-Carrion and Poppel, 2007), drug dependence and abuse (Schultz, 2002; Piercem and Kumaresan 2006; Berridge, 2007; Ikemoto, 2007), pain and analgesia (Wood, 2008), and psychic symptoms (Diaz, 1996; Laviolette, 2007).

It has been demonstrated that the repeated administrations of psychomotor stimulants such as methamphetamine and cocaine as well as narcotic analgesics such as morphine induced sensitization to their ambulation-increasing effect in mice, and that the induction of sensitization could be inhibited when mice were placed in a small jar (6 cm in diameter) after each drug administration (Kuribara and Tadokoro, 1989; Kuribara. 1995a,b, 1996a,b). In such a narrow space, expression of the ambulation (horizontal movement), but not turning and vertical movements, can be perfectly inhibited without blocking the pharmacologi-

cal effect. Furthermore, the present author found that an early post-drug period before attaining to the peak effect was important to induce a significant sensitization to the ambulation-increasing effect of psychomotor stimulants and narcotic analgesics (Kuribara, 1996b, 2009, 2010). The restraint did not block the pharmacological effect of drugs. Such results bring a consideration that a repeated experience of both the pharmacological effect of drug and the resultant ambulation during the early post-drug period is the minimum requirement for induction of the sensitization to ambulation-increasing effect of psychomotor stimulants and narcotic analgesics, i.e., conditioning (learning and memory) of the behavioral output. It is also suggested that the behavioral sensitization is closely related to the dependence liability of drugs (Kuribara and Hirabayashi, 1985; Pert et al., 1990).

Different from the characteristics of the ambulation-increasing effects of psychomotor stimulants and narcotic analgesics, the repeated administration of SCP to the mice at intervals of 1 day or longer resulted in a significant decrease in the ambulation-increasing effect (Kuribara and Tadokoro, 1983, 1987). These results bring a question whether the decrease in the ambulation-increasing effect of SCP is produced by the tolerance to the pharmacological effect of SCP, or by the behavioral tolerance, namely conditioning, dependent on the environmental factors.

The aims of this study were to assess the modification by the environment of the SCP-induced ambulatory stimulation following the repeated administration. The free ambulation of mice was limited after the post-SCP period.

Materials and Methods

Animals

Male mice of the ddY strain (SLA Japan, Hamamatsu) were used when they attained at 6 weeks of age and a weight of 25-28 g. Groups of 10 mice each had been housed in polycarbonate cages (20W × 25L × 15H cm) with free eating a solid diet (MF: Oriental Yeast, Tokyo) and tap water except during the behavioral tests. The conditions of the breeding room were controlled (temperature; 23 ± 1 °C, relative humidity; 55 ± 3 %, and a 12:12-hr light-dark cycle; lights on between 06:00-18:00 hr). The temperature and relative humidity of experimental room were almost the same as the breeding room.

All the experimental treatments mentioned below were carried out according to "*The Guiding Principles for the Care and Use of Laboratory Animals*" of The Japanese Pharmacological Society.

Apparatus

The ambulatory activity of 10 mice was individually and simultaneously measured with "ambulometer" which had 10 tilting-type Plexiglas activity cages of 20 cm in diameter and 15 cm in height (SMA-10: O'hara & Co., Tokyo) (Fig.1). The apparatus selectively detected horizontal movements (ambulation), but not turning, or vertical movements such as rearing, head movement or sniffing, of the mouse.

To selectively restrict the ambulation of mice, glass jars (6 cm in diameter and 15 cm in height) were used. In the jar, the mouse could almost freely express vertical movements and turning.

Drug

The drug used was scopolamine HBr (SCP: Sigma Chemical, St. Louis, MO). SCP was dissolved in physiological saline, and subcutaneously (s.c.) administered at a constant volume of 0.1 ml/10 g body weight of the mouse independent of the doses of SCP. The doses of SCP were expressed in the salt form.

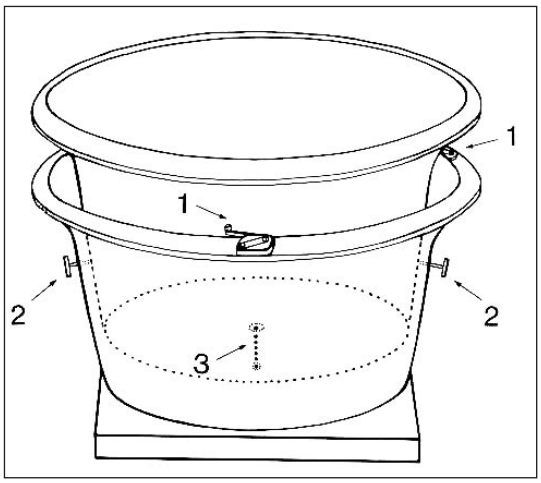

Fig. 1. The ambulometer for selective measurement of horizontal movement of the mouse.
1: Microswitches for detection of the mouse's movement.
2: Stoppers of the activity cage.
3. Falcrum of the activity cage.

Experimental schedules

All the experimental treatments; the administration of SCP, putting the mouse in the glass jar and measurement of ambulation of the mice, were carried out between 09:00-16:00 hr.

In the case of measurement of the activity of mice, they were individually put in the activity cages for 10 min, and then the administration of SCP or saline was conducted. The activity of each mouse was measured at intervals of 10 min for 90 min.

1) Determination of the optimum dose of SCP

Four groups of mice (10 mice each) were administered SCP (0: saline, 0.5, 2 and 8 mg/kg s.c.), and their activity were measured for 90 min.

In addition, the other one group of 10 mice was treated with SCP (2 mg/kg) + free movement for 5 times at intervals of 3 days.

2) Repeated SCP administration with limited ambulation

Ten groups of mice (10 mice each) were given SCP (2 mg/kg), and they were allowed to freely move in the activity cage during the post-SCP period of either 0-10, 0-20, 0-30, 0-60, 10-30, 10-60, 10-90, 30-60, 30-90 or 60-90 min. During the other periods by 90 min after the SCP administration, these mice were individually put into the small jars to restrict their ambulation. As the control administration for SCP, other 10 groups of mice were given saline, and allowed ambulation in the activity cage in the same schedules as in the SCP study. In addition, two sets of 2 groups of mice (10 mice each) were given either SCP or saline, and then put in the activity cages (free ambulation) or in the jars (perfect restraint) for 90 min. Such pretreatments were carried out 5 times at 3-day intervals.

Three days after the final (5th) pretreatment, SCP was challenge-administered to all groups of mice, and their ambulatory activities were measured for 90 min.

Statistical analysis

Since the durations of measurement of the ambulatory activity were different among groups of mice in the pretreatment phase, the mean activity counts in each group were analyzed by one-way analysis of variance (ANOVA). In the challenge administration phase, the data were analyzed by two-way ANOVA. Post-hoc analyses were carried out by Bonferroni test. Values of p less than 0.05 were considered significant.

Results

Time-courses of change in the SCP-induced activity

As shown in Fig. 2, SCP-induced ambulatory stimulation attained to the peak level during the period of 10-20 min, and almost ceased by 90 min after the administration.

Repeated administration of SCP

The repeated administration of SCP (2 mg/kg) induced progressive decrease in the ambulation-increasing effect (Fig. 3). However, no marked change in the latency to the peak effect or duration of the effect was produced.

Table 1 shows the activity counts following five repeated administrations of SCP with limited ambulation during the various post-SCP periods.

The repeated administration of SCP resulted in a significant tolerance to the ambulation-increasing effect in the

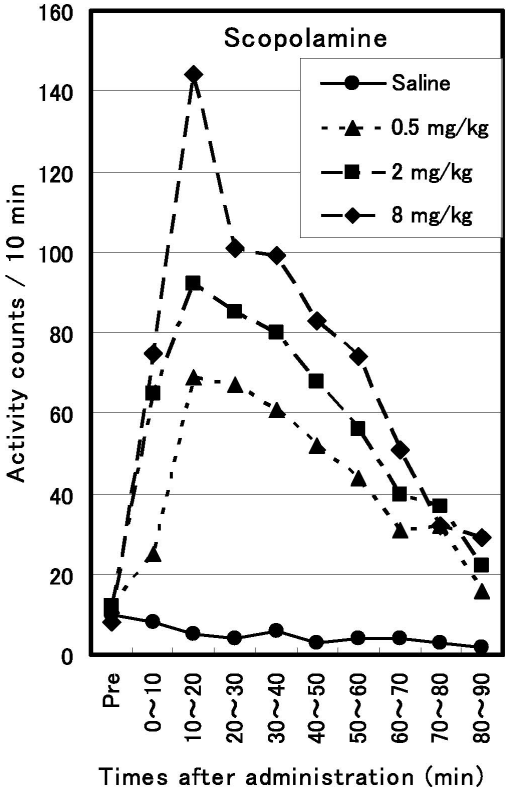

Fig. 2. Time-courses of change in the scopolamine (0: saline, 0.5, 2 and 8 mg/kg s.c.)-induced ambulatory stimulation in mice. N=10 in each group.

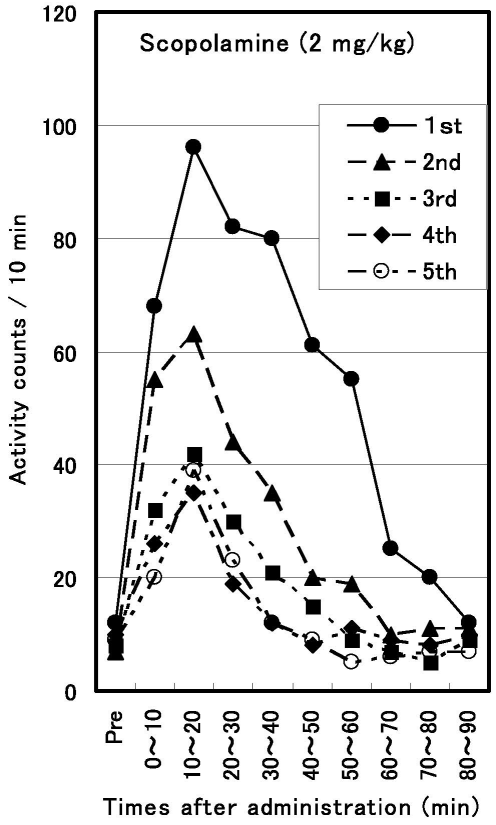

Fig. 3. Time-courses of change in the mean ambulatory activity count following five administrations of scopolamine (2 mg/kg s.c.) at 3-day intervals to the mice. N=10.

groups of mice with free ambulation during post-SCP periods of 10-60min, but not in the groups of mice with free ambulation during post-SCP periods of 0-10 min and 60-90 min. The development of tolerance was much marked in the groups with the free ambulation during the early post-SCP periods of 10-30 min.

The activity of the saline-administered mice with free or limited ambulation were very low (15-68 counts) in the 1st administration, and no significant changes in the activity counts were demonstrated throughout the five repeated administrations (data not shown).

Challenge administration of SCP

Table 2 shows mean 90 min activity counts following the challenge administration of SCP to the groups of mice that had been pretreated with SCP or saline with free or limited ambulation.

The groups of mice pretreated with repeated administration of saline with free or limited ambulation did not show significant change in the sensitivity to challenge administered SCP.

The activity counts in the groups of mice allowed free ambulation during the post-SCP periods of 0-20, 0-30, 0-60, 10-30, 10-60 and 10-90 min were as high as that in the group of mice with no restraint (free ambulation for 90 min). The groups of mice allowed free ambulation during

Table 1. Activity counts after the repeated administration of scopolamine (2 mg/kg s.c.) at 3-day intervals.

Period of free movement	1st	2nd	3rd	4th	5th
0-90min	523±61	262±28*	172±15*	124±15*	106±13*
0-10	72± 7	68± 7	65± 5	55± 6	56± 7
0-20	169±15	112±11*	78± 8*	59± 7*	65± 9*
0-30	260±21	151±17	103±11*	77± 9*	73± 6*
0-60	468±45	218±22*	147±18*	101±11*	74± 7*
10-30	170±13	103± 8*	69± 6*	50± 4*	49± 6*
10-60	393±50	194±26*	131±16*	83±10*	70± 8*
10-90	490±69	221±33*	49±17*	107±15*	109±13*
30-60	202±21	144±18	103± 9*	69± 5*	58± 6*
30-90	299±33	254±22	203±20*	199±15*	156±13*
60-90	85±11	79± 8	73± 6	79±12	72± 9

N=10 in each group. *: $p<0.05$ vs. the 1st administration within each group.

Table 2. Activity counts after the challenge-administration of scopolamine (2mg/kg s.c.) to the mice pretreated with scopolamine (2 mg/kg) or saline + limited ambulation for 5 times at 3-day intervals.

Period of free-movement in the pretreatment sessions	Scopolamine	Saline
0-90 min (No restraint)	96±10*	571±71
0-10	408±79	549±44
0-20	119±11*	511±49
0-30	92±10*	560±59
0-60	105± 7*	505±40
10-30	102±10*	521±51
10-60	90± 7*	559±70
10-90	93±12*	518±64
30-60	399±46*,$	529±46
30-90	401±45*,$	533±42
60-90	520±66$	546±69
Perfect restraint for 90min	580±66$	562±79

N=10 in each group.

*: $p<0.05$ vs. the saline-pretreated group with the same condition of free-movement.

$: $p<0.05$ vs. the mice with SCP + no restraint.

the post-SCP periods of 30-60 and 30-90 min demonstrated partial tolerance. However, the activity count of the group of mice allowed free ambulation during the post-SCP periods of 0-10 min showed a slight, but not significant, decrease in the sensitivity to the challenge-administered SCP. The activity counts of the groups of mice allowed ambulation during the post-SCP periods of 60-90 min and perfectly restricted for 90 min were almost the same as that of the group of mice pretreated with saline with free ambulation.

Discussion

It has been considered that central dopaminergic system (Fink and Morgenstern, 1980) and cholinergic systems (Mathura et al., 1997; Shannon and Peters, 2001; Chintoh et al., 2003) are involved in the SCP-induced hyperactivity. In some cases, a restraint and even handling of mice including injection of drug or saline act as stressors, and result in an increased sensitivity to central acting drugs through a stimulation of central dopaminergic and/or opiate systems (Kalivas and Stewaet, 1991; Deroche et al., 1992; Shaham et al., 1995). However, the mice pretreated with saline with free and limited ambulation, and even with perfect restraint for 90 min did not show any significant change in the sensitivity to challenge-administered SCP, suggesting that the restraint or handling carried out in this study did not alter neurotransmissions of dopaminergic, opiate or cholinergic systems.

Generally, the repeated administrations of psychomotor stimulants and narcotic analgesics to the mice induce significant sensitization to their ambulation-increasing effects, and that the early-post drug period before the peak effect is the essential factor for induction of sensitization to the ambulation-increasing effect (Kuribara, 1995a,b, 1996a,b, 2009, 2010). The mechanisms of behavioral sensitization to psychomotor stimulants and narcotic analgesics are considered to be basically identical, i.e., stimulation of the mesolimbic dopaminergic systems (Van der Heuval and Pasterkamp, 2008; Matsumoto and Hikosaka, 2009) which are strongly related to the reward effects, i.e., dependence liability (Piercem and Kumaresan 2006; Berridge, 2007; Ikemoto, 2007).

Different from the effects of psychomotor stimulants and narcotic analgesics, the repeated administration of SCP to the mice at intervals of 3 days with the free ambulation in the activity cage induced progressive decrease in the ambulation-increasing effect. The chronic treatment of SCP causes an increased sensitivity of cholinergic receptors (Marks et al., 1984). However, such pharmacological tolerance may not be involved in the decreased ambulation-increasing effect demonstrated in the present experiment. The groups of mice pretreated with SCP with perfect restraint for 90 min did not show tolerance to the ambulation-increasing effect of SCP. The restraint selectively blocked the expression of ambulation, but not turning or vertical movements, without inhibiting the pharmacological effects of SCP. It is therefore highly probable that the induction of environment-dependent tolerance to the ambulation-increasing effect of SCP is specific.

It is interesting to note that groups of mice treated with SCP + free ambulation during the post-SCP periods of 0-20, 0-30, 0-60, 10-30, 10-60 and 10-90 min showed progressive decrease in the ambulation-increasing effect, and that the activity counts at the challenge-administration of SCP were as high as that in the group of mice allowed free ambulation for 90 min (no restraint). The groups of mice allowed ambulation during the post-SCP periods of 30-60 and 30-90 min showed partial tolerance. However, the activity counts of the groups of mice perfectly restricted the ambulation for 90 min, or allowed ambulation during the post-SCP periods of 0-10 and 60-90 min were almost the same as that of the group of mice pretreated with saline + free ambulation, showing no tolerance to the ambulation-increasing effect of SCP. These results indicate that the metabolic or functional tolerance to SCP is scarcely involved in the decreased sensitivity to SCP after the repeated administration at 3-day intervals, and that the repeated experience of symptoms produced by the muscarinic anti-cholinergic effect of SCP and ambulation during the post-SCP period of 10-30 min, but not 0-10 or 60-90 min, is an important factor for induction of a significant tolerance to the ambulation-increasing effect of SCP., i.e., environment-dependent tolerance or behavioral tolerance.

These results suggest that, although SCP stimulates central dopaminergic systems through the antagonistic action on the muscarinic cholinergic receptors which may be related to the reward effect of SCP (Glick and Goido, 1982; Rasmussen and Fink-Jensen, 2000), the harmful symptoms caused by muscarinic anti-cholinergic effect is much stronger than the reward effect. Since the restraint in the narrow jar selectively inhibits the ambulation of mice without blocking the muscarinic anti-cholinergic effect of SCP, it is emphasized that the connection of ambulation and the harmful symptoms during post-SCP period of 10-30 min plays extremely important role in the induction of significant decrease in the ambulation-increasing effect following the repeated administration of SCP. Such mechanism may be basically similar to the induction of behavioral sensitization to psychomotor stimulants (Kuribara, 1995b, 1996a, 2009) and narcotic analgesics (Kuribara, 2010), although the directions of the change in the effect are completely opposite.

The present results are also consistent with the evidence that severe dependence and abuse are rare for the muscarinic anti-cholinergic drugs (Sussman and Ames, 2001), although a small number of recreational use of SCP and SCP-containing plant, Angel' s trumpet, for short-term has been reported (Greene et al., 1996; Brunton et al., 2008). The behavioral effect of SCP demonstrated in this study may be related to the psychopharmacological characteristics of SCP that the harmful symptoms such as dry mouth and eyes produced by blockade of parasympathomimetic nervous systems overwhelm the reward effect (dependence liability) of this drug.

Conclusion

A significant decrease in the ambulation-increasing effect of SCP (2 mg/kg s.c.), an antagonist of muscarinic cholinergic receptors, was induced when it was repeatedly administered to mice at intervals of 3 days. When the ambulation of mice was allowed during the post-SCP period of 10-30 min, the tolerance to SCP was perfectly induced. However, the allowance of free ambulation during post-SCP period of 30-60 min was followed by a partial tolerance. Free ambulation during post-SCP period of 0-10 or 60-90 min produced no tolerance. These results suggest that the tolerance to the ambulation-increasing effect of SCP is induced by the connection of the ambulation and the harmful symptoms caused by the stimulation of the parasympathomimetic nervous systems, and that the harmful symptoms overwhelm the reward effect of SCP.

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Scopolamineのマウス移所運動促進作用に対する耐性形成
－投与直後の自由運動の重要性－

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抄録： Scopolamine（2 mg/kg s.c.）は、投与後10-20分の時間帯を最大効果とし、約90分間にわたってマウスの移所運動を促進した。同一用量のscopolamineを3日間隔で反復投与し、直径20 cmの測定容器によって移所運動を測定すると、運動促進効果に対する耐性が引き起こされた。Scopolamineの投与後90分間の間に、一定時間にわたってマウスを測定容器内で、運動を可能とした。それ以外の時間帯は直径6 cmの円筒内に入れて運動を制限した。すると、投与後10～30分の時間帯に測定容器内で運動を許されたマウスは、90分間にわたって自由に運動させたマウスと同程度の耐性形成を示した。一方、30～60分の時間帯に運動を許されたマウスでは部分的な耐性形成にとどまり、0～10分あるいは60～90分の時間帯の運動では耐性形成あるいは増感のいずれも生じなかった。生理食塩水の投与と運動制限の組み合わせは、scopolamineに対する感受性に全く影響しなかった。これらの結果は、scopolamineの投与から10～60分間、特に10～30分間の時間帯における薬物効果と運動の両方を経験することが、マウス移所運動促進効果に対する行動的な耐性形成に必須であることを示している。また、本実験で示されたscopolamineの行動薬理学的特性は、口渇やドライアイといった本薬物の抗コリン作用に起因する嫌悪感がドパミン神経系の刺激で引き起こされる依存性を上回ることを示唆している。
（別刷請求先：栗原　久）

キーワード： Scopolamine、行動的耐性、移所運動の制限、投与後時間、条件付け、嫌悪効果、マウス