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Induction of the Sensitization to Morphine-induced Ambulatory Stimulation in Mice: Importance of Free Movement in the Early Post-Morphine Period

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Abstract: Morphine (10 mg/kg s.c.) accelerated the ambulatory activity of mice for 3 hr with a peak effect around 1/2-1 hr after the administration. A sensitization to the morphine-induced stimulation was produced when the mice were repeatedly given morphine at 3-day intervals, and they were individually put in activity cages of 20 cm in diameter for 3 hr after each administration. The sensitization attained a plateau by the 4th administration, and the 3-hr overall activity counts at the 4th and later administrations were 2.2-2.4 times as high as that at the first administration. However, neither marked change in the latency to the peak effect nor prolongation of the stimulant effect was demonstrated even in the morphine-sensitized mice. The mice allowed ambulation in the activity cages during post-morphine period of 1/2-1 hr showed a strong sensitization as high as that in the mice given morphine with the free ambulation for 3 hr. Whereas, the limited allowance of ambulation during the post-morphine periods of 0-1/2 and 1-3 hr resulted in only partial or no sensitization. The repeated administrations of saline with free or limited ambulation caused no significant change in the sensitivity to morphine. These results suggest that the repeated experience of both morphine effect and the resultant ambulation during the early post-morphine period of 1/2-1 hr, i.e., immediately before the peak effect, highly contributes to the induction of ambulatory sensitization to morphine in mice. This period may be related to the development of the reward effect of narcotic analgesic drugs such as morphine and heroin which is the main factor of abuse and dependence liability.
(Reprint request should be sent to Hisashi Kuribara)

Key words: Morphine, Behavioral sensitization, Limited ambulation, Early post-morphine period, Conditioning, Reward effect, Mice.

Introduction

Morphine, a prototypic drug of narcotic analgesic, has an agonistic action on μ-opioid receptors, and resultantly accelerates dopaminergic neurotransmission (Joyce and Iversen, 1979; Teitelbaum et al., 1979). Mesolimbic dopamine 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; Ikemoto, 2007), drug dependence and abuse (Schultz, 2002; Ikemoto, 2007; Piercem and Kumaresan 2006; Berridge, 2007), pain and analgesia (Wood, 2008), and psychic symptoms (Diaz, 1996; Laviolette, 2007).

In general, drugs are repeatedly administered. It is therefore important to study changes in the drug effects following repeated administrations. When morphine is repeatedly administered with inter-dose intervals of 1 day or longer, a sensitization to the behavioral stimulant effect of morphine is induced in mice (Kuribara and Tadokoro, 1989; Kuribara, 1996c, 2010) and rats (Shaham et al., 1995). It has been considered that changes in the opioid and/or dopaminergic neurotransmission are involved in the induction of behavioral sensitization to morphine (Kalivas and Duffy, 1987; Kalivas and Stewart, 1991). Such a consideration can also be supported by the inhibitory effect of μ-opioid receptor antagonist, naloxone, or dopamine D-2 receptor antagonist, nemonapride, on the induction of ambulatory sensitization to morphine (Kuribara, 1995a).

Furthermore, it has been demonstrated that the sensitization to morphine-induced ambulatory stimulation was inhibited when mice were individually placed in a small jar

(6 cm in diameter) for 3 hr after each administration of morphine (Iizuka and Hirabayashi, 1983). In such a space, the expression of ambulation, but not turning and vertical movements, was perfectly restricted. Of course, the restraint did not block the analgesic effect of morphine. This result brings a hypothesis that a repeated experience of both morphine effect and the resultant ambulation is responsible for the induction of sensitization to the ambulatory stimulant effect of morphine. In the induction of ambulatory sensitization, a free ambulation for 0.5 hr for methamphetamine (Kuribara, 1995, 1996a, b) and for 0.25 hr for cocaine (Kuribara, 2009) in the post-drug period of 0-1 hr is essential. Kuribara (2010) demonstrated that the blockade of morphine effect by naloxone, an opioid receptor blocker, in the post-morphine period of 1/2-1 hr failed to induce the sensitization to the ambulation-increasing effect of morphine. However, it is still unknown the minimum duration of ambulation during the post-morphine period to induce the strong sensitization to morphine.

The aims of this study were to assess the level of sensitization to the ambulatory stimulant effect of morphine in mice that were limited the ambulation during the post-morphine period.

Materials and Methods

Animals

Male mice of the ddY strain (SLA Japan, Hamamatsu) were used 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 access to a solid diet (MF: Oriental Yeast, Tokyo) and tap water. 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).

Apparatus

The ambulation of 10 mice was individually and simultaneously measured with a tilting-type "ambulometer" which had 10 bucket-like Plexiglas activity cages of 20 cm in diameter and 15 cm in height (SMA-10: O' hara & Co., Tokyo). The apparatus detected slight tilts of the activity cage generated by horizontal movements (positional change, i.e., ambulation) of the mouse. Since vertical movements such as rearing, head movement, sniffing etc. as well as turning, which were not related to positional change, did not generate the tilt of the activity cage, occurrences of these behaviors were not recorded with the "ambulometer". Thus, the "ambulometer" could selectively and quantitatively detect the ambulation 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.

Drugs

The drug used was morphine HCl (Takeda Chemicals, Osaka), and the dose was fixed to 10 mg/kg in the salt form. The dose of morphine was considered to be optimum for induction of sensitization to the ambulatory stimulant effect of morphine (Iizuka and Hirabayashi, 1983; Kuribara and Tadokoro, 1989; Kuribara, 1995a, 2010). Morphine was dissolved with physiological saline, and subcutaneously (s.c.) administered at a constant volume of 0.1 ml/10 g body weight of the mouse.

Experimental schedules

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

Seventeen groups of mice (10 mice each) were given morphine, and they were allowed to freely move in the activity cage during the post-morphine period of either 0-1/12, 0-1/4, 0-1/2, 0-1, 0-2, 1/2-3, 1-3, 3/2-3, 2-3, 5/2-3, 1/2-1, 1-3/2, 3/2-2, 2-5/2, 1/2-3/2, 1-2 or 3/2-5/2 hr. During the other periods by 3 hr after the morphine administration, these mice were individually kept in the small jar to restrict their ambulation. As the control administration for morphine, other 17 groups of mice were given saline, and allowed to move for limited periods in the activity cage in the same schedules as in morphine study. Furthermore, two sets of 2 groups of mice (10 mice each) were given either saline or morphine, and then kept in the activity cages (free ambulation) or in the jars (perfect restraint) for 3 hr. Such pretreatments were carried out 3 times at 3-day intervals. Three days after the final pretreatment, morphine was challenge-administered to all groups of mice, and their ambulatory activities were measured for 3 hr.

Ethical consideration for experimental animals

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

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

Repeated administration of morphine

Morphine-induced ambulatory stimulation attained to the peak level during the pose-morphine period of 1/2-1 hr, and ceased by 3 hr after the administration. The ambulatory sensitization was much marked during the post-morphine period of 1/2-1 hr, and the sensitization attained plateau by the fourth administration. However, no prolongation of the ambulatory stimulant effect was demonstrated even after induction of the ambulatory sensitization.

Table 1 shows the activity counts following three repeated administrations of morphine with limited ambulation during the various post-morphine periods. The repeated administration of morphine with free ambulation for 3 hr, or limited ambulation during post-morphine period of either 0-1, 0-2, 1/2-3, 1-3, 3/2-3, 2-3, 1/2-1, 1-3/2, 3/2-2, 1/2-5/2 or 1-2 hr resulted in significant enhancement of the activity counts. However, the mice given morphine with limited ambulation during the other post-morphine periods of 0-1/12, 0-1/4, 0-1/2, 5/2-3, 2-5/2 and 3/2-5/2 hr did not show significant enhancement of the activity counts.

On the other hand, the activity of mice that were repeatedly given saline with free or limited ambulation were very low (18-86 counts), and no significant change in the activity count was demonstrated throughout the three repeated administrations (data not shown).

Table 1. Mean activity counts following 3 repeated administrations of morphine (10 mg/kg s.c.) with limited ambulation during various post-morphine periods.

Period of free Ambulation	Repeated administration		
	1st	2nd	3rd
0 – 1/12 hr	12 ± 2	9 ± 2	10 ± 2
0 – 1/4 hr	57 ± 9	69 ± 13	57 ± 13
0 – 1/2 hr	298 ± 54	344 ± 66	413 ± 88
0 – 1 hr	788 ± 181	1068 ± 203	1383 ± 276*
0 – 2 hr	1417 ± 338	2454 ± 361	3191 ± 514*
1/2 – 3 hr	1350 ± 183	1568 ± 139	2154 ± 198*
1 – 3 hr	767 ± 110	916 ± 122	1269 ± 268*
3/2 – 3 hr	331 ± 76	558 ± 163	613 ± 149*
2 – 3 hr	222 ± 34	292 ± 42	358 ± 73*
5/2 – 3 hr	112 ± 29	138 ± 36	139 ± 26
1/2 – 1 hr	563 ± 85	870 ± 144*	1022 ± 167*
1 – 3/2 hr	432 ± 66	636 ± 123	796 ± 151*
3/2 – 2 hr	160 ± 47	220 ± 24	286 ± 56*
2 – 5/2 hr	181 ± 36	260 ± 52	243 ± 31
1/2 – 3/2 hr	1086 ± 120	1969 ± 141*	2180 ± 200*
1 – 2 hr	454 ± 95	1076 ± 118*	1166 ± 143*
3/2 - 5/2 hr	277 ± 39	339 ± 51	347 ± 67
Free ambulation	1548 ± 147	2346 ± 179*	3399 ± 255*

Morphine was administered 3 times at 3-day intervals. The restraint was carried out by placing the mouse in a glass jar (6 cm in diameter and 15 cm in height). Each value is mean activity count ± SEM of 10 mice during period of free ambulation. *: $p<0.05$ vs. the value at the first administration within each group of mice.

Challenge administration

Table 2 shows mean 3-hr activity counts following the challenge administration of morphine to the groups of mice that had been pretreated with morphine or saline with free or limited ambulation. The groups of mice pretreated with three repeated administration of saline with free or limited ambulation did not show significant change in the sensitivity to the challenge-administered morphine. In contrast, the activity counts following the challenge-administered morphine in the groups of mice allowed ambulation during the post-morphine periods of 0-1, 0-2, 1/2-1, 1/2-3/2 and 1/2-3 hr were as high as that in the group of mice allowed free ambulation for 3 hr. The groups of mice allowed ambulation during the post-morphine periods of 1-3/2, 1-2, 1-3, 3/2-2, 3/2-5/2, 3/2-3 and 2-3 hr demonstrated a partial sensitization. However, the groups of mice allowed ambulation during the post-morphine periods of 0-1/12, 0-1/4, 1-1/2, 2-5/2 and 5/2-3 hr, and the group of mice restricted the ambulation for 3 hr did not show sensitization nor tolerance, and the activity counts in these groups of mice were almost the same as that of the group of mice pretreated with saline with free ambulation.

Gross observation

The mice in the glass jar did not show any behaviors concerning to strong stress such as vocalization, excess defecation or urination, etc. Morphine did not produce any stereotyped behavior such as sniffing or pivotting in all mice.

Discussion

Previous experiments demonstrated that the repeated administration of morphine, six times at 3-day intervals with the free ambulation in the activity cage, elicited significant sensitization to the ambulatory stimulant effect, and an enhancement of the stimulant effect attained plateau by the fourth administration (Kuribara and Tadokoro,

Table 2. Mean 3-hr activity counts after the challenge-administration of morphine (10 mg/kg s.c.) to the mice experienced the limited ambulation during the post-morphine or -saline period.

Period of free Ambulation	Drugs administered in the pretreatment session	
	Morphine	Saline
0 – 1/12 hr	1490 ± 122	1522 ± 108
0 – 1/4 hr	1511 ± 123	1487 ± 107
0 – 1/2 hr	1707 ± 148	1501 ± 98
0 – 1 hr	3271 ± 308*	1498 ± 117
0 – 2 hr	3408 ± 295*	1396 ± 121
1/2 – 3 hr	3317 ± 253*	1431 ± 103
1 – 3 hr	2418 ± 191*,$	1453 ± 94
3/2 – 3 hr	2521 ± 209*,$	1504 ± 118
2 – 3 hr	2301 ± 173*,$	1550 ± 111
5/2 – 3 hr	1639 ± 133	1473 ± 106
1/2 – 1 hr	3352 ± 331*	1449 ± 84
1 – 3/2 hr	2711 ± 203*,$	1490 ± 107
3/2 – 2 hr	2491 ± 177*,$	1472 ± 96
2 – 5/2 hr	2290 ± 182*,$	1549 ± 104
1/2 – 3/2 hr	3470 ± 332*	1426 ± 83
1 – 2 hr	2653 ± 209*,$	1456 ± 95
3/2 – 5/2 hr	2290 ± 177*,$	1435 ± 113
No restraint (0-3 hr)	3350 ± 264	1489 ± 107
Perfect restraint	1381 ± 121	1458 ± 99

In the pretreatment sessions, morphine or saline was administered 3 times at 3-day intervals.
The restraint was carried out by putting the mouse in a glass jar (6 cm in diameter and 15 cm in height).
The challenge-administration of morphine was conducted 3 days after the third pretreatment.
Each value is mean activity count ± SEM of 10 mice for 3 hr after the challenge administration of morphine.
*: $p<0.05$ vs. the value of the group given saline in the same experimental condition.
$: $p<0.05$ vs. the value of the group given morphine with free ambulation.

1989; Kuribara, 1995a, 2010). Even though the sensitization to the stimulant effect was induced by the repeated administration of morphine, the time course of changes in the morphine-induced stimulation of ambulatory activity was qualitatively the same, and no marked change in the latency to the peak effect and no prolongation of the effect were demonstrated throughout the repeated administrations. According to these basic results, in this experiment, the repeated administrations of morphine were carried out three times at 3-day intervals, and the challenge-administration of morphine was conducted 3 days after the third pretreatment.

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 morphine (Kalivas and Stewart, 1987; Leyton and Stewart, 1990; Deroche et al., 1992; Shaham et al., 1995). However, the mice pretreated with saline with free or limited ambulation, and even with restraint for 3 hr did not show any significant change in sensitivity to challenge-administered morphine, suggesting that the restraint and handling carried out in this study did not alter neurotransmissions which were related to modification of sensitivity to morphine. The facts that mice given morphine or saline in the jar did not show any behaviors concerning to stress such as vocalization, excess defecation or urination also support this consideration.

In consistent with the previous report (Iizuka and Hirabayashi, 1983), the groups of mice pretreated with morphine with restraint for 3 hr did not show sensitization to the ambulatory stimulant effect of morphine. The restraint selectively blocked the expression of ambulation, but not turning and vertical movements, without inhibiting the pharmacological effect of morphine. Thus, the context-dependent induction of sensitization to the ambulatory stimulant effect of morphine is almost the same as following the repeated administrations of psychostimulants such as amphetamines (Hirabayashi and Alam, 1981; Post et al., 1981; Stewart and Vezina, 1988).

Furthermore, it is interesting to note that groups of mice pretreated with morphine with limited ambulation during post-morphine periods of 0-1, 0-2, 1/2-3, 1/2-1 and 1/2-3/2 hr, but not other groups, showed increased sensitivity to morphine as strong as that demonstrated by the group of mice given morphine with free ambulation for 3 hr. Kuribara (2010) have demonstrated that the blockade of morphine effect by naloxone, an opioid receptor blocker, in the post-morphine period of 1/2-1 hr failed to induce the sensitization to the ambulatory stimulant effect of morphine. These results indicate that a repeated experience of pharmacological effect of morphine and resultant ambulation during post-morphine period of 1/2-1 hr is essential for induction of a strong sensitization to the ambulatory stimulant effect of morphine. In contrast, the ambulation during the other post-morphine periods, i.e., later post-morphine period, may play less contribution to the induction of sensitization to morphine. These thought can be supported by the time course of change in morphine-induced ambulatory stimulation. The enhancement of ambulatory stimulation was much marked in the post-morphine period of 1/2-1 hr (i.e., around the peak effect), but comparatively less during the later post-morphine periods. Since the restraint did not block the pharmacological effect of morphine, it is stressed that the ambulation during the peak effect is important for conditioning of ambulatory sensitization to morphine. The ambulation during the early post-drug period is also important for the induction of the sensitization to the ambulatory stimulant effect of methamphetamine (Kuribara, 1995b, 1996a) and cocaine (Kuribara, 2009). It is therefore considered that the mechanisms of sensitization to morphine, methamphetamine and cocaine are basically identical, i.e., stimulation of the mesolimbic dopamine system (Van der Heuval and Pasterkamp, 2008; Matsumoto and Hikosaka, 2009) which is strongly related to the reward effects (Piercem and Kumaresan 2006; Ikemoto, 2007; Berridge, 2007).

It has been reported that environmental conditions play important roles in the potentials of the abuse liability of psychostimulants (Stewart, 1992) and on the induction of psychopathological symptoms caused by repeated abuse of psychostimulants (Vezina and Stewart, 1984; Pert et al., 1990). Moreover, the liability of behavioral sensitization to psychostimulants as well as narcotic analgesics is considered to be intimately related to the liability of drug abuse (Wise and Bozarth, 1987).

It is therefore probable that the characteristics of environment-dependent sensitization to the ambulatory stimulant effect of morphine may explain the effect of environmental factors on the induction and maintenance of morphine abuse.

The present experiments demonstrated that the sensitization to morphine was induced in the mice which experienced the free ambulation under the CNS stimulant effect of morphine in the early post-morphine period of 1/2-1 hr. This result might be related to the development of the reward effect of morphine, which is essential factor for induction and maintenance of abuse.

Conclusion

A significant sensitization to the ambulatory stimulant effect of morphine (10 mg/kg s.c.), an opioid receptor agonist, was induced when it was repeatedly administered to mice at intervals of 3 days. When the free ambulation was restricted by putting the mouse in a glass jar with 6 cm in diameter in the post-morphine period of 1/2 hr and later partially, and at 0-1/3 hr and later period perfectly inhibited the induction of the sensitization to morphine. However, the restriction of free ambulation in the post-morphine period of 3/4 hr and later could not block the morphine sensitization. These results suggest that the simultaneous experience of the central effect of morphine and the resultant ambulation for 1/2 hr prior to the peak effect is important for induction of the sensitization to the ambulatory stimulant effect of morphine in mice. It is also indicated that the reward effect of morphine appears in the early post-morphine period prior to the peak effect.

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マウスの移所運動からみたモルヒネ増感現象の誘発
－最大効果到達前の運動経験の重要性－

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抄録： モルヒネ（10 mg/kg s.c.）は、1/2～1時間後を最大効果とし、約3時間にわたってマウスの移所運動を促進した。同一用量のモルヒネを3日間隔で反復投与して直径20 cmの測定容器によって移所運動を測定すると、4回目投与まで進行的な効果増強が発現し、初回投与時の2.2～2.4倍に達した。しかし、最大効果の到達時間および効果持続時間に変化はなかった。モルヒネ投与後、一定時間にわたりマウスを測定容器内で運動を可能とし、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。投与後1/2～1時間の時間帯に測定容器内で運動を許されたマウスは、3時間にわたって自由に運動させてマウスと同程度の増感を示した。一方、0～1/2時間、1～3時間の時間帯に運動を許されたマウスでは、増感現象が認められなかった。生理食塩水の投与と運動制限の組み合わせは、モルヒネ感受性に全く影響しなかった。これらの結果は、モルヒネの投与から1/2～1時間の比較的早い段階、つまり最大効果発現直前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、モルヒネのマウス移所運動促進効果に対する増感現象の発現に必須であることを示している。この時間帯は、モルヒネやヘロインといった麻薬性鎮痛薬の乱用・依存を誘発する報酬効果の発現時間とも関連すると考えられる。
（別刷請求先：栗原　久）

キーワード： モルヒネ、行動的増感現象、移所運動の制限、投与後時間、条件付け、報酬的効果、マウス