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Behavioral Characteristics Following Lesions of the Nucleus Accumbens Septi in Rats

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ABSTRACT

Caudal, rostral and both areas of the nucleus accumbens septi (NAB) were lesioned each in separate animal group by applying DC of 3.0 mA for 15 sec. in order to examine if any regional differences in the NAB with regard to the manifestation of locomotor activity. The r-NAB and cr-NAB-lesioned rats were significantly increased in locomotor activity but not in the c-NAB-lesioned rats and the effect following the NAB lesion was immediately produced and returned to control levels in about 7 days postoperatively. On the other hand, the locomotor stimulation produced by methamphetamine was significantly attenuated in all NAB-lesioned rats but also stereotyped behavior was significantly elicited simultaneously. These results thus suggested that NAB may be attributed to the inhibitory role in the locomotor activity, of which intensity differs from rostral site and caudal site, and stereotyped behavior may be shown higher sensitivity of the denervated striatal dopamine function.

Key Words: nucleus accumbens septi, methamphetamine, dopamine, locomotor activities
Abbreviation: NAB; nucleus accumbens septi, A; anterior, L; lateral, V; ventral, MA; methamphetamine, DA; dopamine

INTRODUCTION

Cerebral catecholamines are reported to be involved in the control of locomotor activity (Green & Grahame-Smith, 1974; Segal & Mandell, 1970). The nucleus accumbens septi (NAB) is widely accepted to be a major mesolimbic nucleus containing dopaminergic terminals (Simon *et al.*, 1976; Ungerstedt, 1971) and much work has clearly indicated that NAB plays an important role on the locomotor activity (Costall *et al.*, 1979; Kelly *et al.*, 1975; Lee, 1984). On the other hand, amphetamine seems to act indirectly by releasing catecholamines and/or inhibiting its reuptake (Carlsson, 1970; Weissman *et al.*, 1966) and it was reported that a dopamine mechanism in the NAB was very important in hyperactivity induced by amphetamine (Kelly *et al.*, 1975; Thornburg & Moore, 1973). Recently, it has been present in the NAB dependent on the site. Nevertheless, there would not be subjected to any detailed investigation for exploring the relation between local lesions of the NAB and behavioral differences.

The present study was undertaken to elucidate the functional difference within the NAB with regard to the manifestation of locomotor activity by examing the effects of partial lesion in the caudal site, rostral site and both sites of the NAB.

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METHOD

Animals

The employed animals were male Wistar King A rats with an average weight of 220 ± 10 g at the time of surgery. The rats were group-housed (4/cage) throughout the experimental period and were given food and water *ad libitum*. These animals were maintained at room temperature of 22 ± 1°C and were on a 12 hours light-dark schedule (light on at 07:00, off at 19:00).

Surgical procedure

The animals were anesthetized with sodium pentobarbital (40 mg/kg i.p.) and the head was fixed in a stereotaxic instruments. Monopolar electrodes composed of stainless steel wire of 0.2 mm in diameter and insulated except for the last 0.5 mm of the tips were inserted into different sites of the NAB. Three types of bilateral lesions of the NAB, i.e., lesions of caudal site of the NAB (c-NAB: anterior(A), 8.6; lateral(L), 1.5; ventral(V),-1.4), rostral site of the NAB (r-NAB: A, 9.6; L, 1.0; V,-0.9) and both c-NAB and r-NAB were made according to König and Klippel's brain atlas (König & Klippel, 1963), respectively. Each lesion was made by applying DC of 3.0 mA for 15 sec. Sham operated rats underwent the same surgical procedure except insertion of electrodes. After the operation each animal was given an intramuscular injection of procaine penicillin G.

Testing procedure

Following either sham operation or brain lesions, one group of the rats were measured in the changes of spontaneous behaviors in the openfield apparatus. Another group of the rats were given 3 mg/kg of methamphetamine hydrochloride dissolved in 0.9 % salion solution, intraperitioneally and then were observed in the changes of behaviors. The items of the tests belong to the locomotor activity (the numbers of blocks traversed in the open-field apparatus), rearing (upstanding position) and stereotyped behavior (continuous repetition of purposeless motor acts). The control values of these items in each group were measured prior to the surgery. The tests were performed 2, 7, 15 and 30 days postoperatively.

Apparatus

The Hall's open-field apparatus (Hall, 1934) was employed. The floor was divided into 19 blocks of approximately equal width with painted line and illuminated by a 100 W light placed 80 cm above the center.

Histology and statistical analysis

After completion of all experiments the animals were anesthetized with ether and their brains were perfused with 10 % formalin through the carotid arteries. The brain was removed, fixed and 50-60 μm frozen sections were prepared and stained with cresyl violet. The site and extent of the brain lesions were verified histologically. The results were statistically analyzed using Mann-Whitney U-test for the locomotor activity and Fisher's exact probability test for the incidence of stereotyped behavior.

RESULTS

Histology

In animals subjected to c-NAB lesions, extensive areas from anterior 8.3 to 8.9 were lesioned and extensive areas from anterior 8.9 to 10.0 were lesioned in r-NAB lesions. In cr-NAB lesions, the lesions extended quite extensive area from anterior 8.3 to 10.0 and spread out toward the latero-medial NAB (Fig. 1).

General observation

NAB-lesioned rats displayed high reactivity when they were first handled on the second postoperative day. But such irritability was gradually decreased and no significant difference was found between NAB-lesioned and sham rats 15 days after surgery. On the other hand, NAB-lesioned rats showed no significant differences in body weight, urination and defecation as compared with sham rats.

Changes in locomotor activity

The locomotor activity in the NAB-lesioned rats was shown in Fig. 2. c-NAB rats (n = 8) not showed

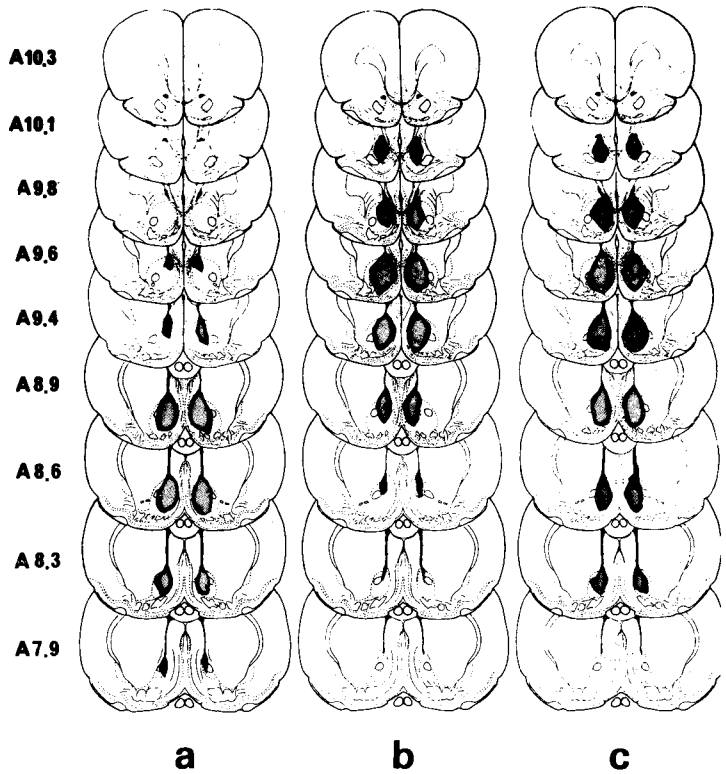

Fig. 1. Diagrammatic representation of the location and extent of lesions in: (a) caudal site of the nucleus accumbens septi (c-NAB); (b) rostral site of the nucleus accumbens septi (r-NAB); and (c) both caudal and rostral sites of the nucleus accumbens septi (cr-NAB). Each diagram, constructed from histological data obtained from 8 to 9 rats. Frontal section, adapted from König and Klippels atlas. Stippled shading, lesioned sites observed in all of the rats. Black shading, damaged sites observed occasionally in the sections examined.

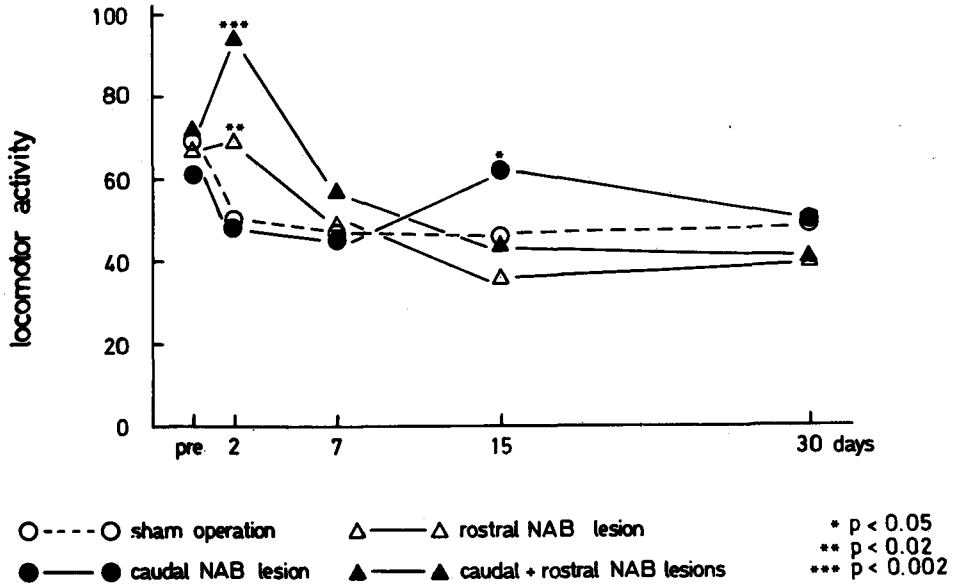

Fig. 2. Effects of the nucleus accumbens septi lesions on locomotor activity in rats (open-field test).

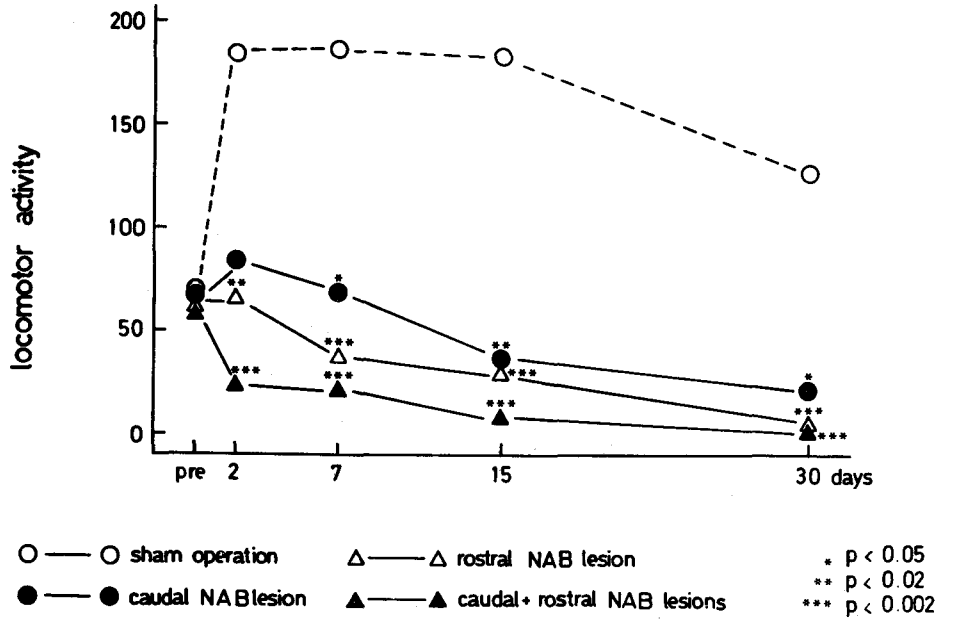

Fig. 3. Changes of the methamphetamine-induced hyperactivity following lesions of the nucleus accumbens septi in rats.

a significant change in locomotor activity throughout the experimental period except 15 days ($p<0.05$) after surgery. r-NAB rats ($n=8$) and cr-NAB rats ($n=8$) were significantly increased in locomotor activity 2 days (r-NAB: $p<0.02$, cr-NAB: $p<0.002$) postoperatively, as compared with sham rats. In addition, it was noticed that hyperactivity of cr-NAB rats was significantly increased as compared with not

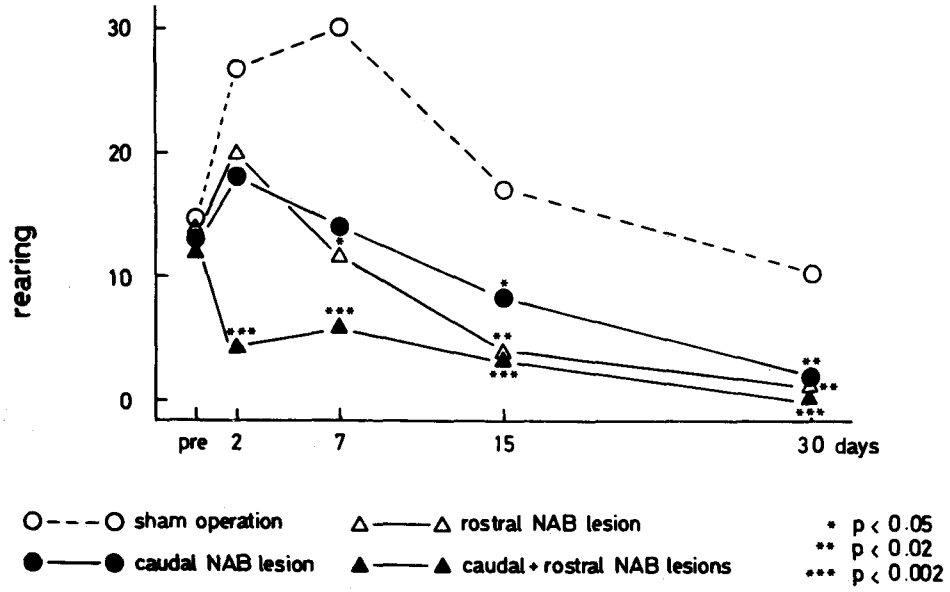

Fig. 4. Changes of the methamphetamine-induced rearing following lesions of the nucleus accumbens septi in rats.

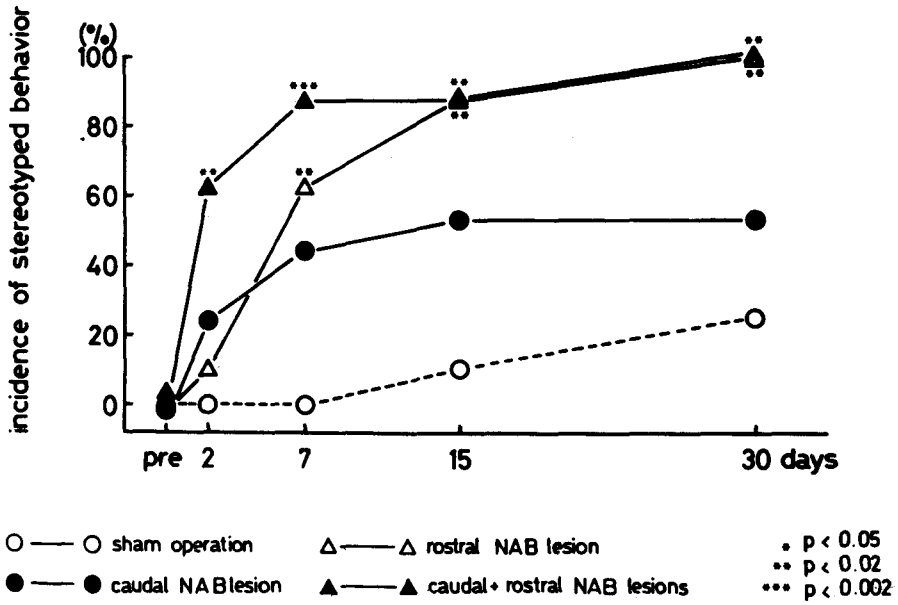

Fig. 5. Incidence of the methamphetamine-induced stereotyped behavior following lesions of the nucleus accumbens septi in rats.

only sham rats ($p<0.002$) but also c-NAB rats ($p<0.05$) 2 days after surgery.

However, hyperactivity of the r-NAB rats gradually reduced and no significant difference 7 days after operation, as compared with sham rats. On the other hand, rearing of the c-NAB rats was significant-

ly increased only 15 days after surgery as well as locomotor activity ($p<0.05$). Rearing of the r-NAB rats was not changed throughout the experimental period and cr-NAB rats was significantly increased 2 and 7 days (both: $p<0.05$) after surgery.

As illustrated in Fig. 3 all three types of NAB lesions showed a significant difference in the effect of the locomotor stimulation produced by methamphetamine hydrochloride (MA) as compared with sham rats. Sham rats ($n=8$) were remarkably increased in locomotor activity by MA and persisted throughout the experimental period. However, none of the NAB-lesioned rats showed a significant increase of the locomotor activity by MA. c-NAB rats were significantly decreased in the locomotor activity except 2 days (7, 15 days: $p<0.05$, 10 days: $p<0.02$), and r-NAB rats and cr-NAB rats were significantly decreased throughout the experimental period (r-NAB: 2 days; $p<0.05$, besides; $p<0.02$, cr-NAB: all; $p<0.02$). The NAB-lesioned rats showed a significant difference in the rearing as well as locomotor activity after injecting MA as compared with sham rats (Fig. 4). On the other hand, NAB-lesioned rats produced significantly high incidence of stereotyped behavior, in addition to remarkable hypoactivity after injecting MA (Fig. 5).

Stereotyped behavior was induced by all the three types of NAB lesions, although the incidence in each group was quiet different, and persisted throughout experimental period. Significant differences in the incidences of stereotyped behavior between sham rats and NAB-lesioned rats were found in the r-NAB (7, 15 and 30 days: all; $p<0.02$) and cr-NAB rats (2, 15 and 30 days: $p<0.02$, 7 days: $p<0.002$) but not in the c-NAB rats.

DISCUSSION

The present study shows that bilateral lesion in cr-NAB produced a significant increase locomotor activity. Rorens *et al.* (1970) also reported that the lesion of the NAB increased the activity level. These results suggested that the NAB plays an inhibitory role in the control of locomotor activity.

On the other hand, the increase in locomotor activity was significant both r-NAB and cr-NAB-lesioned rats but not c-NAB-lesioned rats as compared with sham rats. This result indicated that rostral site is more important than caudal site with the manifestation of motor function. Also, the test period, although the reason is not known, may be important for modulation of motor function since the changes of locomotor activity were found only during the earlier period (within the 5 day) following the lesion in this and other studies (Iversen *et al.*, 1975; Lorens *et al.*, 1970).

In this experiment, all of sham rats showed a significant increase in locomotor activity by 3 mg/kg of MA, but not induced steretyped behavior. However, all the three types of NAB lesion rats did not produce hyperactivity by MA instead of significant decrease in locomotor activity. Increased exploration or locomotor activity is the most prominent signs of the low doses of amphetamine in rodents. Amphetamine seems to act indirectly by releasing catecholamine and/or inhibiting its reuptake and the NAB has been considered to be an important site of hyperactivity induced by amphetamine. Many studies have reported that the main catecholamine of the NAB is dopamine (Simon *et al.*, 1976; Ungerstedt, 1971). The dopaminergic innervation of NAB is important in the locomotor stimulation produced by MA, since this stimulation is induced by bilateral injection of dopamine and dopamine agonists directly into the NAB (Costall *et al.*, 1979; Lee, 1984), and blocked by bilateral 6-OHDA lesions of the NAB (Kelly & Iversen, 1976, Kelly *et al.*, 1975). In this respect, it seemed that hypoactivity following the electrolytic NAB lesion was correlated with decrease of the NAB dopaminergic level, although in this present experiment, no quantitative difference was found following lesion of c-NAB, r-NAB and cr-NAB. In addition, it is noticed that NAB-lesioned rats produced not only hypoactivity but also induced high incidence of stereotyped behavior. Dopamine is principally localized in two systems of neurons in CNS, i.e., the nigrostriatal dopaminergic system from the substantia nigra to the corpus striatum and mesolimbic dopaminergic system from other portion of the midbrain to the

olfactory tubercle, nucleus accumbens, related limbic areas and the frontal cortex (Ungerstedt, 1971). It has been reported that the locomotor stimulation elicited by low doses of MA is responsible for mesolimbic DA system and the stereotyped behavior produced by high doses of MA is responsible for nigrostriatal DA system. In this regards, the intence stereotyped behavior produced by 3 mg/kg of MA following the NAB lesions may be characterized by the striatal DA system rather than NAB DA system. Moreover, it has been reported that striatal DA level was significantly reduced following the NAB lesion (Lee, 1984). These results suggested that stereotyped behavior produced by MA in the NAB-lesioned rats may be attributed higher sensitivity to the denervated striatal DA function.

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=국문초록=

측좌각의 부위별 파괴가 행동에 미치는 영향

충남대학교 약학대학 약학과

이 순 철

측좌각의 형태학적 특성에 따른 측좌각의 전반부 후반부 그리고 전반부와 후반부를 동시에 파괴하는 3종류의 동물군이 15초간 3.0mA의 직류전류를 통하여 이루어졌다.

자발운동의 관찰에 있어서 측좌각의 전반부 파괴군과 전후반부 동시 파괴군은 현저한 자발운동의 증가를 나타내었으나 후반부 파괴군은 별다른 변화를 나타내지 않았다. 또한 측좌각 파괴후 나타나는 자발운동의 변화는 파괴후 즉시 나타났으며 약 1주일 경과 후에는 대조군과 유사하게 되었다.

한편, 대조군에서는 메타암페타민의 자발운동 흥분효과가 현저하게 나타났으나 측좌각 파괴군에서는 전반부 후반부 그리고 전후반부 동시파괴군 등 3종류의 파괴군 모두에서 흥분효과가 전혀 나타나지 않았으며 그와 동시에 상동 행동의 발현률이 유의성있게 나타났다.

이상 결과는 측좌각이 자발운동에 있어서 억제적으로 작용하나 전반부와 후반부의 역활이 같지 않음을 시사하고 있으며 상동행동의 발현은 측좌각 도파민보다는 선조체 도파민의 기능변화에 기인되는 것으로 사료되었다.