

아편양 순응제가 백서의 억제된 자발적 교대행동에 미치는 영향*

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Effects of Opioid Agonists on the Suppressed Spontaneous Alternation Behaviour in Rats*

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ABSTRACT

This study was designed to evaluate the effects of opioid receptor agonists on the spontaneous alternation behaviour in an animal model of obsessive-compulsive disorder in rats. According to the theory that dopamine is related to the biological etiology of obsessive-compulsive disorder, the effect of the nalbuphine (opioid kappa agonist) and the tramadol (opioid mu agonist), which act as manipulating agents on the inhibition or stimulation of dopamine release, in the spontaneous alternation behaviour were evaluated.

24 hours prior to the experiment, rats were food-deprived. These rats were put into the T-maze, in which white and black goal boxes were baited with small amounts of chocolate milk. Each rat was given 2 set of 7 trials during which it was placed in the start box and allowed to choose the one of the goal boxes for each time. After identifying the stable baseline of spontaneous alternation behaviour, nonselective 5-HT agonist 5-MeODMT (1.25mg/kg/IP) disrupted spontaneous alternation. Rats were stratified into fluoxetine (10mg/kg/IP), nalbuphine (10mg/kg/IP), tramadol (46.4mg/kg/IP), and saline (0.5cc/IP) injection group with experimental drug treatment for 21 days. The effects on the 5-MeODMT (1.25mg/kg/IP) induced disruption of spontaneous alternation behaviour were checked at the next day of discontinuation of drug treatment.

The results were as follows ;

- 1) At the day after 21 days of the drug treatment, the nalbuphine treated group and the fluoxetine treated group showed significant difference from the tramadol treated group and the saline treated group in the 5-MeODMT (1.25mg/kg/IP) induced suppression of spontaneous alternation behaviour.
- 2) Within each drug treatment group, the fluoxetine treated group showed significant difference between before and after the treatment of fluoxetine in the 5-MeODMT (1.25mg/kg/IP) induced suppression of spontaneous alternation behaviour. And also, the nalbuphine treated group showed significant difference between before and after the treatment of nalbuphine in the 5-MeODMT (1.25mg/kg/IP) induced suppression of spontaneous alternation behaviour. There was no difference between the baseline and after the treatment of nalbuphine in the 5-MeODMT (1.25mg/kg/IP) induced suppression of spontaneous alternation behaviour.

We identified that the opioid kappa agonist that act as dopamine release inhibitor affect the spontaneous alternation behaviour which is an animal model of obsessive-compulsive disorder in rat.

KEY WORDS : Opioid receptor agonists · Animal model · Spontaneous alternation behaviour.

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서 론

가 (March 1993 ; Meltzer 1979 ; Pitman 1991).

가 가 가 (Flament 1987 ; Greist 1995 ; Jenike 1990).

clomipramine desmethylclomipramine (Insel 1983).

desmet - hylclomipramine 가 (Insel 1983).

5 - hydroxy - indoleacetic acid serotonin (Flament 1987 ; Thoren 1980).

(SSRI) 50% serotonin 가 (McDougle 1993).

가 가 (Goodman 1990 ; Sharp 1987)

가 (Stahl 1996). Jibson (1990) homovanillic acid 5 - hydroxyindoleacetic acid 가 (Jibson 1990).

SSRI 가 (Goodman 1990).

1/3 (Sharp 1987).

가 (Goodman 1990). clomipramine (Austin 1991 ; Leonard Rapoport 1989).

fluoxetine homovanillic acid 가 fluoxetine (Meltzer 1979).

(1997 ; Bouchard 1989 ; Brod 1989 ; Tate 1989).

fluoxetine

가 가

Insel Pickar(1980) 2 op - iate naloxone opiate 가 Saphira (1997) SSRI opioid mu tramadol

Opiates , , , , , , (periaqueductal) , , , (Fields 1993).

opioid (Morhan Mikhail 1996). Opiate , , , substance P (Wonnacott 1995).

opioid pep - tide (Wonnacott 1995).

guinea pig kappa (Wonnacott 1995). (caudate nucleus) mu delta 가 (Westerink 1995).

(arcuate nucleus) delta , mu (Longoni 1991).

opioid kappa nalbuphine mu tramadol

opioid kappa (nalbuphine) mu (spontaneous alter - nation behaviour : SAB)

연구 방법

1. 실험재료
- 1) 실험동물

Sprague - Dawley

14
 20 24 (42 × 26
 × 18cm) 3 8 12

200 250gm 4 8

2) 강박행동 동물모형
 SAB

Montgomery(1952)가

T -

가 (rim) ×
 × : 10 × 50 × 15cm가

15cm가 T -

85cm (1).

3) 실험약물

(1) 5 - MeODMT (5 - methoxy - N,N - dimet -
 hyltryptamine : Sigma), fluoxetine(Lilly)
 , nalbuphine(10mg/ml :)
 tramadol(50mg/ml :)

(2)

(SAB)
 5 - MeODMT 1.25mg/kg (Ya -
 din 1991). fluoxetine
 (1997), Yadin (1991), Woods (1993)
 10mg/kg . Nalbuphine

(Walker Young
 1993) 10mg/kg . Tr -
 amadol

가 가
 46.4mg/kg (Frink 1996).

가 21

21

(Ha -

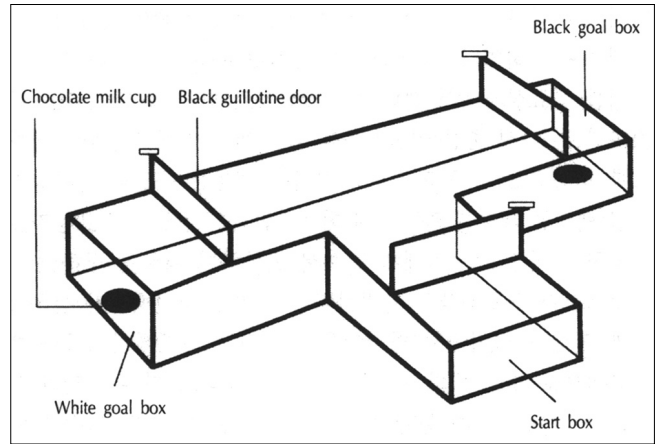


Fig. 1. A picture model of the apparatus for spontaneous alternation behaviour.

ddock 1989 ; Yadin 1991).

2. 실험절차

1) 자발적 교대 행동 훈련(Spontaneous alternation training)

Montgomery(1952)가

24

가

T -

20

5

T -

가

가

가

, 10 가

가

7

가

SAB

1 7

(ma -

ximum latency) 90, 90, SAB
 1.28 ± 0.28 (1).

46 SAB
 6 가 90
 2) 5-MeODMT 투여로 유발된 강박행동
 SAB ()
 5 5 - MeODMT (1.25mg/kg)
 5 - MeODMT (1.25mg/kg/IP) 5

2. 5-MeODMT 투여에 의한 SAB 억제 효과
 SAB () 5 - MeODMT
 (1.25mg/kg) 5
 SAB 3.76 ± 1.32 15
 SAB 3.53 ± 1.03 5 - Me -
 ODMT (1.25mg/kg/IP) 5, 15
 1.28 ± 0.28 (1).

15
 3) 실험약물 투여
 5 - MeODMT SAB가 fluoxe -
 tine(N = 10), nalbuphine(N = 10), tramadol(N = 9), saline(N
 = 10) 21 4
 6
 21 1
 39

, 5 - MeODMT (1.25mg/kg/IP) 5 15
 SAB 3.64 ± 0.91 SAB
 (1.28 ± 0.28) 2.8 가
 (t = - 16.32, p < .0001)
 (1).
 5 - MeODMT (1.25mg/kg)
 SAB

4) 실험약물의 만성투여가 5-MeODMT 투여로 억제된 SAB
 에 미치는 효과
 21 22
 5 - MeODMT (1.25mg/kg/IP) 5 15

3. 각 약물투여군에서 5-MeODMT 투여로 유발된 강박행동
 에 미치는 효과
 5 - MeODMT (1.25mg/kg/IP) 5
 nalbuphine (1.60 ± 0.46) fluoxetine (1.80 ±
 0.79) tramadol (3.33 ± 0.83) saline (3.
 35 ± 0.34) nalbuphine
 fluoxetine 5 - MeODMT (1.25mg/kg/IP)
 SAB 5 - MeODMT
 (1.25mg/kg/IP) 15 nalbuphine
 (1.30 ± 0.35) fluoxetine (2.00 ± 0.82)
 tramadol (3.50 ± 1.22) saline (3.55 ± 0.28)
 nalbuphine fluoxe -
 tine 5 - MeODMT SAB
 (2).

3. 통계처리
 SPSS - PC for window 7.5
 , 5 - MeODMT (1.25mg/kg/
 IP) SAB 21
 5 - MeODMT (1.25mg/kg/IP)
 Scheffe
 5 - MeODMT (1.25mg/kg/IP)
 SAB 21 5 - Me - ODMT (1.25
 mg/kg/IP) SAB
 p < .01

4. 각 약물 투여군에서 SAB 훈련 기준치와 실험약물 투여
 전후의 5-MeODMT 투여에 따른 SAB의 변화
 1) Fluoxetine (N = 10) SAB (1.30 ±
 0.26) 5 - MeODMT (1.25mg/kg/IP)
 SAB (3.80 ± 1.38) , fluoxetine 21
 5 - MeODMT (1.25mg/kg/IP) SAB

결 과

1. 자발적 교대 행동의 훈련(Spontaneous alternation tr-
 aining) 기준치
 7 2

Table 1. Comparisons of the numbers of repetitive choices between the baseline and after the 5-MeODMT treatment

	Baseline (N=39)	5-MeODMT(N=39)	t
Number of choices	1.28 ± 0.28	3.64 ± 0.91	- 16.32*
Paired t-test	*p < .01		

Table 2. Comparisons of the numbers of repetitive choice 5 and 15 minutes after injection of 5-MeODMT after 21 days of drug treatment among four experimental groups (Mean ± SD)

Group	5-MeODMT Injection	
	After 5 Min.	After 15 Min
Fluoxetine (N=10)	1.80 ± 0.79	2.00 ± 0.82 ^{b*}
Nalbuphine (N=10)	1.60 ± 0.46	1.30 ± 0.35 ^{a*}
Tramadol (N= 9)	3.33 ± 0.83	3.50 ± 1.22 ^c
Saline (N=10)	3.35 ± 0.34	3.55 ± 0.28 ^d

a,b<c,d
*p<.01 by oneway-ANOVA

Table 3. Comparisons of the numbers of repetitive choices among baseline, before and after 21 days of drug treatment in 5-MeODMT treatment sessions among four experimental groups (Mean ± SD)

Group	Baseline	5-MeODMT	
		Before drug treatment	21 days after drug treatment
Fluoxetine (N=10)	1.30 ± 0.26 ^a	3.80 ± 1.38 ^b	1.90 ± 0.40 ^c
Nalbuphine (N=10)	1.30 ± 0.35 ^a	3.72 ± 0.98 ^b	1.45 ± 0.28 ^c
Tramadol (N= 9)	1.33 ± 0.25 ^a	3.61 ± 0.64 ^b	3.42 ± 0.79 ^c
Saline (N=10)	1.20 ± 0.26 ^a	3.43 ± 0.39 ^b	3.45 ± 0.26 ^c

a,c < b : nalbuphine treated group*
a < c < b : fluoxetine treated group*
a < c, b : tramadol treated group*, saline control*
p < .01 by MANOVA, General linear model procedure

(1.90 ± 0.40) SAB
Fluoxetine 가
5 - MeODMT(1.25mg/kg/IP)
2) Nalbuphine (N=10) SAB (1.30 ± 0.35) 5 - MeODMT(1.25mg/kg/IP) SAB (3.72 ± 0.98) , nalbuphine 21 5 - MeODMT(1.25mg/kg/IP) nalbuphine 가 SAB (1.45 ± 0.28) 5 - MeODMT(1.25mg/kg/IP) 가 nalbuphine 가 3) Tramadol (N=9) SAB (1.33 ± 0.25) 5 - MeODMT(1.25mg/kg/IP) SAB (3.61 ± 0.64) , tramadol 21 5 - MeODMT(1.25mg/kg/IP) SAB (3.42 ± 0.79) tra - madol 5 - MeODMT(1.25mg/kg/IP) 가 4) Saline (N=10) SAB (1.20 ± 0.26) 5 - MeODMT(1.25mg/kg/IP) SAB (3.43 ± 0.39) , saline 21 5 - MeODMT(1.25mg/kg/IP) SAB (3.45 ± 0.26) SAB 5 - MeODMT(1.25mg/kg/IP)가 (3).
고 찰
opioid 1984). , opioid (Leckman

1995). opioid peptide , , GABA (Lec - kman 1995). opiate (Wise Rapoport 1989). Haber Wolfer(1992) 가 dynorphin 가 (von Economo 1931). Laplane (1984) 가 . Mu kappa morphine (Pfaus Go - rzalka 1987). - endorphin op - ioid가 (Kaye 1987 ; Kaye 1982). Opiates가 , ka - ppa synapsin I synapsin II adenyI cyclase가 mu adenyI cyclase 가 (Wonnacott 1995). Opiates가 (Alper 1980), (Wood 1982), (Yonehara Clouet 1984), (Matthews Ger - man 1984) . (Mulder 1984). , opiate가

1984). (Mulder opioid MeODMT(1.25mg/kg/IP) (3.64 ± 0.91)
5 - MeODMT(1.25mg/kg/IP)가
(Wolgin SAB .
1985). (1997) Yadin (1991) 5 - MeODMT(1.25
Opiate , mg/kg/IP) SAB .
(Kalivas 1983). fluoxetine(10mg/kg) 5 -
opiates가 MeODMT(1.25mg/kg/IP) 3.80 ± 1.38
(Tang Collins 1985). , 21 fluoxetine(10mg/kg)
opiates가 5 - MeODMT(1.25mg/kg/IP) 1.90 ± 0.39 SAB
Opiates
, mu (Fontaine Chouinard 1985 ; Kokkinidis Anisman
가 (Wonnacott 1995). , 1976 ; Yadin 1991). fluoxe -
opiate , tine
delta 가 (Wonn - (Fontaine Cho -
acott 1995). mu delta uinard 1985 ; Kokkinidis Anisman 1976 ; Yadin 1991).
, mu Nalbuphine(10mg/kg) 5 - MeODMT
(Wonnacott 1995). (1.25mg/kg/IP) (3.72 ± 0.98)
, opiates , 21 nalbuphine(10mg/kg) 5 -
, opiates MeODMT(1.25mg/kg/IP) (1.45 ± 1.45) SAB
substance P . SAB (1.30 ± 0.
(Dugan Fleetwood - Walker 1993). 35) 가 T -
opiates가 SAB nalbuphine 가
. Elwan Soliman(1995) opiates
T - , , ,
(SAB) . Pitman(1991) D₁, D₂ . Yakim -
ovskii(1995) enkephaline
가
amphetamine enkephaline .
haloperidol (Pi - Callahan (1996)
tman 1991). mu 가 kappa
, opiates가
(Pato 1997). opioid kappa
SAB nalbuphine SAB
T - 2 . Nalbuphine kappa
가 (Montgomery 1952). mu (Sch -
SAB midt 1985). Nalbuphine
(Kokkinidis Anisman 1976 ; Yadin 1991). SAB
SAB 가 SAB
가 (Richman 1987).
Yadin (1991) SAB Tramadol (46.4mg/kg) 5 - MeODMT
(1.28 ± 0.28) 5 - (1.25mg/kg/IP) 3.56 ± 0.81

21 MeODMT (1.25mg/kg/IP) tramadol (46.4mg/kg) 3.42 ± 0.79 5 - SAB mu 가 (Callahan 1996 ; Elwan Soliman 1995). tramadol SSRI Saphira (1997) opiate 가 opiate 가

결 론

nalbuphine tramadol SAB 5 - Me - ODMT 21 SSRI fluoxetine 21 5 - MeODMT (1.25mg/kg/IP) SAB()

1) 5 - MeODMT (1.25mg/kg/IP) , nalbuphine fluoxetine tramadol saline SAB 5 - MeODMT (1.25mg/kg/IP) IP) SAB

2) 5 - MeODMT (1.25mg/kg/IP) , 5 - MeODMT (1.25mg/kg/IP) SAB nalbuphine 5 - MeODMT (1.25 mg/kg/IP) SAB , fluoxetine 5 - MeODMT (1.25mg/kg/IP) SAB , 가 . tramadol saline 5 - MeODMT (1.25mg/kg /IP) SAB

SAB nalbuphine, fluoxetine . opiod kappa nalbup - hine ,

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