

정신분열병과 병적 노화의 연관성 : 동물모형을 이용한 행동 및 조직학적 연구*

전진숙**† · 오병훈*** · 장환일****

Association of Schizophrenia with Pathological Aging : A Behavioral and Histological Study Using Animal Model*

Jin-Sook Cheon, M.D.,**† Byoung-Hoon Oh, M.D.,*** Hwan-II Chang, M.D.****

ABSTRACT

Objectives : Phencyclidine(PCP) or PCP-like substances such as ketamine have been known to rekindle the cognitive dysfunction in schizophrenia. The aims of this study were to identify whether PCP-like substances can produce cognitive deficit in schizophrenia, to discuss relation with aging process, and finally to speculate underlying neurochemical mechanisms by various drug responses.

Methods : In experiment I, radial maze tests were done in 24 Sprague-Dawley rats for 3 days to get baseline data. Being divided into 4 groups(6 rats respectively) of normal aged, normal adult controls, atropine-treated and ketamine-treated, the radial maze tests were repeated on every week for 6 weeks, and then the rats were sacrificed by intracardiac perfusion with phosphate-buffered 10% formaldehyde solution for histology. The brain specimen was stained with hematoxylin-eosin to count cells in the prefrontal cortex and hippocampus. In experiment II, radial maze tests were done for 48 rats before any drug treatment and only after ketamine administration. Thereafter, haloperidol, bromocriptine, clonidine, nimodipine, tacrine, valproic acid, naloxone and fluoxetine were intramuscularly injected on every other day in addition to ketamine. Radial maze tests were repeated on every week for 6 weeks, and then rats were prepared by the same procedure for histology.

Results : 1) Reaction times of radial maze tests of atropine-treated rats were significantly prolonged than those of normal aged($p<0.05$) or normal adult controls($p<0.05$). Cell numbers of prefrontal cortex & hippocampus in ketamine-treated rats were significantly reduced than those in normal aged ($p<0.05$) or normal adult controls($p<0.005$). 2) Reduced cell numbers by ketamine became significantly raised by tacrine administration in prefrontal cortex & hippocampus($p<0.05$), while there were no significant changes on radial maze tests. Cell numbers also tended to be raised by nimodipine, fluoxetine and haloperidol administration.

Conclusions : In conclusion, the visuospatial memory disorders in ketamine-induced psychotic rats might be partly associated with aging process. Furthermore, the responses to the various drugs suggested cholinergic system might have an important role in the neurochemical mechanism of the cognitive dysfunction in ketamine-induced psychosis. Otherwise, calcium metabolism as well as serotonergic and dopaminergic systems seemed to be possibly related.

KEY WORDS : Ketamine · Visuospatial memory disorders · Aging · Radial maze tests · Prefrontal cortex · Acetylcholine.

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Department of Neuropsychiatry, Kosin University, School of Medicine, Pusan, Korea

Department of Neuropsychiatry, Yonsei University, College of Medicine, Seoul, Korea

Department of Neuropsychiatry, Kyunghee University, Medical College, Seoul, Korea

† : , 602 - 702 34) (051) 250 - 5070/240 - 6245,) (051) 241 - 5069

서론

1956 phencyclidine(PCP) , ketamine
 PCP 가 ,
 arylcycloalkylamines ketamine PCP -
 ketam - 가 가 가 가 . ,
 ine .
 PCP 1950
 (Kornetsky Markowitz “ ” 가 .
 1978 ; Geyer Markou 1995) , PCP . , PCP -
 가
 가 (Bowers 1987), PCP . ,
 (Balster 1987)
 PCP 1979
 catecholamines, acetylcholine,
 (Jo -
 hnson 1987). PCP
 dopaminergic agonist , nicotinic
 muscarinic cholinergic , - methyl -
 D - aspartate(NMDA) ,
 noradrenergic serotonergic
 (Gorelick Balster 1995). Bunney (1995)
 PCP glutamatergic - NMDA ion channel
 glutamate NMDA
 , PCP amphetamine
 amphetamine
 Glutamate , ,
 (Altamura
 1993). Ketamine 가
 가
 (Marcoux 1988). Glutamate
 , PCP -
 가 ,
 PCP
 Ketamine 30 1
 PCP PCP arylcyclohexylamines
 (Zukin Javitt 1991). (Koek 1989)

PCP PCP -

가 . ,

가 가 가

“ ”

, PCP

가 . ,

가 . ,

(Jo -

대상 및 방법

1. 실험동물

200~300gm Sprague - Dawley
 18 400~500gm Sprague - Da -
 wley 6 , 24
 1 , 15% 3%
 I : 24 Sprague - Dawley
 (N=6), (N=6), atropine (N
 =6), ketamine (N=6) 4
 II : 48 Sprague - Dawley 6
 8 ketamine haloperidol,
 valproate, naloxone, nimodipine, tacrine, clonidine, bromo -
 criptine, fluoxetine

2. 연구방법

1) 정신분열병의 동물모형

Ketamine 30 1
 PCP PCP arylcyclohexylamines
 (Koek 1989)

Table 1. Directly observable behavioral activities induced by PCP or PCP-like substances in rodents(Koek et al 1989)

Activity	Description
Locomotion	Locomotion with all four legs moving, for at least 3sec
Rearing	Rearing, with the head at least 5cm above the cage floor
Sniffing	Sniffing, for at least 5sec
Climbing	Climbing the cage wall, with the hind legs not touching the cage floor
Grooming	Grooming with fore paws or hind paws
Gnawing	Gnawing on cage, for at least 3sec
Swaying	Swaying movements of the head(and upper torso) from side to side for at least one complete cycle(ie, left-right-left)
Falling	Falling from a rearing or standing position backwards or to the side
Straub tail	Tail in an erect position
Flat body	Flat body posture, with hind legs splayed
Tremor	Tremor of the head and/or body

(1). 6

2) 방사형 미로 제작 10 2 , 30
1cm 10cm, platform 30cm, 60 , cutoff point 5
45cm, 13cm , phosphate
, 10% chloral hydrate
100gm 60mg , phosphate
buffered 10% formaldehyde

3) 예비실험
1 (food deprivation) , platf -
orm 15 (2) II
, 200mg (food pellet) 48 3
pellet (Buremovi 4 8 keta -
Buremovi (feeder) 가 pe - mine(4mg/100gm) haloperidol(0.75mg/100gm), val -
llet 4 , 가 proate(3mg/100gm), naloxone(0.15mg/100gm), nimodipine
, 200gm (0.004mg/100gm), tacrine(4mg/100gm), clonidine(0.025mg/
pellet 2~3 , 2 100gm) 6 100gm), bromocriptine(0.375mg/100gm), fluoxetine(2.5mg/
, 가 . 6 , 6

4) 본실험
(1) I 5) 조직검사
6 18 3 10% chloral hydrate
, 4 4 100gm 60mg , phosphate
, atropine buffered 10% formaldehyde(9g NaCl, 4g sodium dihydr -
pine , ketamine atropine ogen phosphate - 1 - hydrate, 8.25g disodium hydrogen ph -
100gm 0.2mg atropine osphate - 2 - hydrate, 900ml , 100ml 37.5% formalin
30 , 60 , 90 , 120 stock solution) (intracardiac perfusion)
, Ketamine 100gm 1mg, , 24
2mg, 4mg ketamine ,
(paraplast embedding) , microtome
, 4μm 가 가 1500μm
6 , 3 hematoxylin - eosin

(× 400)

(layer III - IV) (CA1 CA3
,) (nucleolus)

6) 통계분석

Minitab Release 6.1.1. -

(Minitab 1987) SPSS for Windows Release 5.0.1 (SP-
SS 1989~1992) . Ketamine

(ANOVA)

, atropine ketamine

p<0.05

Scheffe

. 4

Pearson

4

(MANOVA)

. Ketamine

t

결 과

1. Ketamine 급성투여 효과

Ketamine 100gm 1mg 30~60
260.2 ± 97.
6 , 100gm 2mg 255.0 ± 11.2 , 100gm
4mg 164.2 ± 108.6 가

(p=0.241)(2).

Atropine
(241.6 ± 83.9) (102.2 ± 31.0)
(95.2 ± 84.1)

(p<0.05)(3). Ketamine 100gm 4mg

30 1
(164.2 ± 108.6) atropine
가 (3).

, , atropine ketam -

Table 2. Comparison of total reaction times on radial maze tests according to the dose changes

Dose of Ketamine	Mean ± SD(Sec)
1mg/100gm(N=6)	260.2 ± 97.6
2mg/100gm(N=6)	255.0 ± 110.2
4mg/100gm(N=6)	164.2 ± 108.6

. Statistically non-significant by one-way ANOVA

Table 3. Comparison of total reaction times on radial maze tests between normal adults, normal aged controls, atropine-treated and ketamine-treated rats

	Mean ± SD(Sec)
Adult controls(N=6)	102.2 ± 31.0
Aged controls(N=6)	95.2 ± 84.1
Atropine-treated(N=6)	241.6 ± 83.9
Ketamine-treated(N=6)	164.2 ± 108.6

*p<0.05 by one-way ANOVA and Scheffe's multiple comparison tests

Table 4. Correlation coefficients(g) among total reaction times on radial maze tests of normal adults, aged controls, atropine-treated and ketamine-treated rats

	Adult	Aged	Atropine	Ketamine
Adult controls	1.000	-0.341	-0.531	-0.047
Aged controls		1.000	0.324	0.775
Atropine-treated			1.000	0.580
Ketamine-treated				1.000

. Statistically non-significant by Pearson's product moment correlation

ine

, ketamine

(=0.775), ketamine

atropine

(=0.580)

(4).

2. Ketamine 만성투여 효과

Ketamine 100gm 4mg 6
6 , , atropine ketamine
, atro -

pine (284.6 ± 34.3)

가 , (214.2 ±
118.6), (175.8 ± 118.6) (5).

6 ketamine

가 , atropine ,

(6). Ketamine

(40.8 ± 8.8 /HPF), CA1(37.3 ± 15.6

/HPF) CA3(36.7 ± 5.9 /HPF) ,

(98.5 ± 32.7 /HPF)

(181.4 ± 51.5 /HPF), CA1(81.0 ± 14.4 /HPF), CA3(64.0

, no -
 repinephrine(NE), dopamine(DA), acetylcholine
 (Ach), serotonin(5 - HT), GABA 가
 (0.05~0.1mg/kg)
 (Johnson 1987). PCP glutamat -
 ergic - NMDA ion channel glutamate
 (Luby (locus ceruleus) NE
 DA
 1959). PCP LSD
 , DA . Acetylcholinesterase
 (proprioception) , muscarinic Ach , Ach
 PCP 5 - HT 5 - HT₂
 가 ,
 PCP NMDA -
 , PCP/ - opiate NMDA
 channel
 (Javitt 1987). PCP ketamine N - methyl - D - asp -
 artate(NMDA)
 Ach NE NMDA -
 , DA ,
 PCP GABA
 GABA
 glutamate (Sagratella 1992).
 glutamate DA
 glutamate , glutamate
 (1998 ; Do 1995). van Kammen
 (1993) GABA가
 glutamate DA/GABA
 benzodiazepine DA, NE GABAa
 PCP (Da -
 vis 1988). Piercey Ray(1988) PCP가
 (anterior cingulate) DA
 DA
 (nucleus accumbens)
 (ventral tegmental area, VTA)
 PCP
 , kainic acid GABA
 glutamic acid decarboxylase(GAD)가 (Ceci
 French 1989). Gundlach (1986) PCP
 가 , PCP
 , PCP amphetamine
 DA, NE, 5 - HT 가 ,
 NMDA - Ach , - opioids
 . Okuyama (1995) PCP
 ,
 2. 정신분열병에서 인지장애의 신경화학적 기전
 PCP PCP

, no -
 repinephrine(NE), dopamine(DA), acetylcholine
 (Ach), serotonin(5 - HT), GABA 가
 (0.05~0.1mg/kg)
 (Johnson 1987). PCP glutamat -
 ergic - NMDA ion channel glutamate
 (Luby (locus ceruleus) NE
 DA
 1959). PCP LSD
 , DA . Acetylcholinesterase
 (proprioception) , muscarinic Ach , Ach
 PCP 5 - HT 5 - HT₂
 가 ,
 PCP NMDA -
 , PCP/ - opiate NMDA
 channel
 (Javitt 1987). PCP ketamine N - methyl - D - asp -
 artate(NMDA)
 Ach NE NMDA -
 , DA ,
 PCP GABA
 GABA
 glutamate (Sagratella 1992).
 glutamate DA
 glutamate , glutamate
 (1998 ; Do 1995). van Kammen
 (1993) GABA가
 glutamate DA/GABA
 benzodiazepine DA, NE GABAa
 PCP (Da -
 vis 1988). Piercey Ray(1988) PCP가
 (anterior cingulate) DA
 DA
 (nucleus accumbens)
 (ventral tegmental area, VTA)
 PCP
 , kainic acid GABA
 glutamic acid decarboxylase(GAD)가 (Ceci
 French 1989). Gundlach (1986) PCP
 가 , PCP
 , PCP amphetamine
 DA, NE, 5 - HT 가 ,
 NMDA - Ach , - opioids
 . Okuyama (1995) PCP
 ,
 2. 정신분열병에서 인지장애의 신경화학적 기전
 PCP PCP

NE - 100, ketamine -

sigma₁, NMDA, chan -

nel, Vincent (1979) PCP, HT, DA, calcium, 가, 5 -

, opiate, PCP, muscarinic

Zukin, Zukin(1979) muscarinic, [³H]PCP (Faustman 1988 ; Gold Harvey

, PCP, 1993 ; Javitt 1995).

glycine, GABA, glutamate, DA, 5 - HT, NE, DA

Rao (1989) PCP가, (pyriform) (Goldberg Gold 1995). To -

DA 가, PCP NE, 5 - HT, Ach mer Flor - Henry(1989) 가 DA

. Noda (1995) DA 가

PCP 5 - HT_{2A}

NMDA PCP (tardive dyskinesia)가 (Davis 1992 ;

MK - 801 VTA DA Waddington 1987).

가, clozapine risperidone 5 - HT₂ 가

₁ - adrenoceptor Rupniak Iversen(1993) DA

PCP (Svensson, NE 가, catecholamine

1995).

PCP NMDA (Le -

ander 1988a ; Leander 1988b ; Rogawski 1988) 3. 정신분열병에서 인지장애와 병적 노화의 연관성

1988 ; Koshikawa 1988). (Yi 가(Cohen 1988)

NMDA glycine (Goldstein 1991 ; Harris 1991 ; Karson 1990). Pr -

(Thomas 1988 ; Lind - ohovnik (1993) 50 Al -

enmayer 1995). øye (1992) ketamine zheimer

NMDA, μ 51%, 28%,

Alzheimer

lcium, NMDA channel ca - 가

(neuroplasticity) (long - 가

term potentiation) neu - Alz - 50

ropeptide가 Alzheimer Alzh -

(Gabriel 1996). eimer Davidson

가, (1996) Alzheimer

amate 가, glut - test) (constructional praxis),

amate, glut - (delayed word recall test)

. Alzheimer

. Shinitzky (1991)

가

ketamine

tacrine 가, nim - P₃₀₀

odipine, fluoxetine haloperidol 가 (O'Donnell 1995).

결론

Alzheimer (fibrillary gliosis)가 (Bruton 1990). Phencyclidine(PCP) ketamine PCP

entorhinal cortex가 (Buckley PCP 1994 ; Goldsmith Joyce 1995 ; Murray 1994 ; Stevens 1982 ; Syvälahti 1994). Sprague - Dawley 24 6 ketamine

(Arnold 1995). 3 , atropine 6

excitotoxin 4 phosphate - buffered 10% formaldehyde H & E 48

glutamate(Abe 1983 ; Boden 1986 ; Gratton 1979 ; Jackson Usherwood 1988 ; Kawai 1982) . 2

Bonhaus (1990) , ketamine ,

NMDA ketamine haloperidol, bromocriptine, clonidine, nimodipine, tacrine, valproic acid, naloxone, fluoxetine 6

NMDA - Rupniak (1991) PCP 0.1~0.2mg/kg scopolamine 6 , 6

rhesus monkey -adrenergic clonidine , naloxone Alzhe - imer Ach, NE, 5 - HT, GABA, NMDA neur - opeptide가 . Cohen(1990) atropine ketamine (p<0.05) (p<0.05)

DA Purohit (1993) Alzheimer (senile plaque) (p<0.005) ketamine (p<0.05)

(neurofibrillary tangle) Alzheimer 2) 2 ketamine tacrine (p<0.05)

가 Atropine modipine, fluoxetine haloperidol ni - Ketamine

ketamine , ketamine acetylcholine 가 calcium serotonin atropine 가 dopamine 가

ketamine , ketamine

중심 단어 :

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