

## Mirtazapine 치료가 여자 우울증 환자의 해마 대사물질에 미치는 영향

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### ABSTRACT

#### Effects of Mirtazapine on Hippocampal Metabolites of Female Patients with Major Depression

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**Objective :** Recent studies suggested that the neurotrophic effects might be a major therapeutic mechanism of antidepressants. However, these effects have not been confirmed yet in depressed patients. We investigated whether mirtazapine treatment has the neurotrophic effects in depressed patient by using <sup>1</sup>H-MRS and explored the relationship between these effects and clinical improvements and neuropsychological functions. **Methods :** Fourteen female, right-handed patients with major depressive disorder and 12 healthy controls participated in the study. Before the treatment with mirtazapine, we measured severity of illness, neuropsychological functions, and the levels of NAA, Cho and Cr in both hippocampi using <sup>1</sup>H-MRS in the depressed subjects. After the treatment with mirtazapine for 6 weeks, we repeated the measures of the pretreatment condition in the depressed subjects. We also measured variables of severity of illness and hippocampal metabolites with <sup>1</sup>H-MRS in the control group. **Results :** There were no significant differences in NAA/Cr, Cho/Cr, and Cho/NAA between the depressed subjects and the control group. However, after the treatment with mirtazapine, there were significant improvements in severity of illness, immediate memory, and delayed memory. The posttreatment ratio of the total hippocampal Cho/Cr was significantly lowered than the ratio of the pretreatment Cho/Cr. However, the percent changes of the hippocampal Cho/Cr from the pretreatment Cho/Cr ratio were not correlated with the changes of severity of illness or neuropsychological functions from the pretreatment condition. **Conclusions :** These findings indicate that mirtazapine may reduce the level of choline metabolites by stabilizing the effect on the cholinergic neurons,

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reducing turnover or metabolism of neuronal membranes, or modulating the neuroendocrine systems in the depressed patients. However, this effect is not necessarily related to clinical improvements. Further studies on the therapeutic action of mirtazapine are needed. (Korean J Psychopharmacol 2005;16(2):146-155)

**KEY WORDS :** Major depression · Mirtazapine · Magnetic resonance spectroscopy · Choline · Hippocampus.

## 서론

phosphocholine(Pcho), glycerophosphocholine (GPCho), phosphatidylcholine(PtdCho), sphingomyelin, choline, acetylcholine

가

1,2)

13,15-17) Cr

NAA, Cho

13,18,19)

가

3-8)

(hypothalamic - pituitary - adrenal axis, HPA axis)

가

9-11)

가

가

가

가

가

20-25)

가

가

(electroconvulsive therapy, ECT)

12,13)

20,21)

(<sup>1</sup>H - Magnetic Resonance Spectroscopy, <sup>1</sup>H - MRS)

가

N - acetyl - L - aspartate(NAA, 2.02 ppm), choline containing compounds(Cho, 3.20 ppm), creatine(Cr, 3.03 ppm)

NAA

(neuroaxonal)

NAA

2A

1A

NAA

12-14) Cho

26)

mirtazapine

가

1A

, 27-29)

가  
mirtazapine

Institutional Review Board(IRB)

mirtazapine 가

가

가

가

가

## 2. 임상 상태 및 신경인지기능 평가

17 HDRS<sup>26)</sup>

Beck (Beck Depression Inventory, BDI)<sup>33)</sup>

가

(Korean - Wechsler Adult

Intelligence Scale - Revised, K - WAIS)<sup>34)</sup>

## 연구대상 및 방법

### 1. 연구대상

1) 18-55

, 2)

, 3) Diagnostic

and Statistical Manual of Mental Disorders(DSM) -<sup>30)</sup>

, 4) St-

ructured Clinical Interview for DSM (SCID - )<sup>31)</sup>

, 5) 17

가 (Hamilton Depression Rating

Scale, HDRS)<sup>32)</sup> 가 19

, 6)

1

(psychotropic medication)

가 (Wechsler Memory Scale, WMS) 3

,<sup>35,36)</sup> Rey - Kim

(Rey - Auditory - Verbal

Learning Test, AVLTL ; Rey - Osterrieth Complex

Figure Test, RCFT)<sup>37,38)</sup> 가

Color Trails

Test(CTT)<sup>39)</sup>

. 6

mirtazapine

### 3. Mirtazapine 치료

6

mirtazapine

tazapine

15~45 mg

lorazepam

mirtazapine

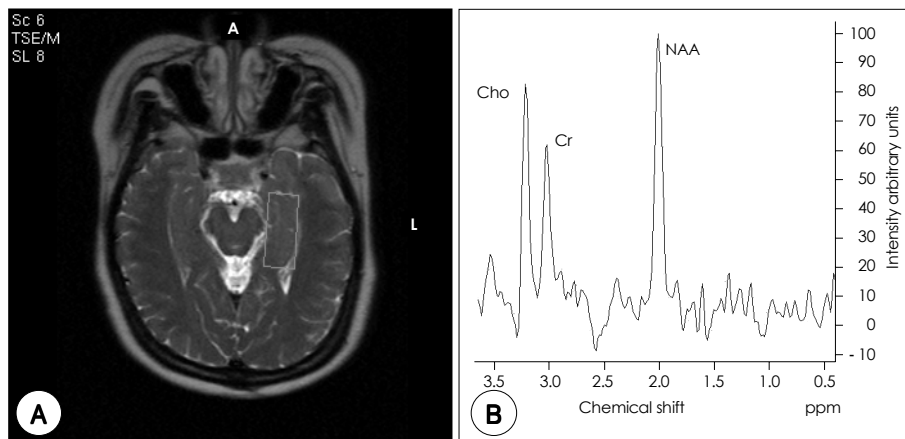
### 4. 양성자 자기공명분광의 측정

1.5

Tesla

(Gyrosan, Phillips Me-

dical System, Best, Netherlands) synergy head coil (1). Voxel Point Resolved Spectroscopy(PRESS) pulse sequence (TR, 2,000 msec ; TE, 272 msec ; number of excitation, 128).  
 가 가 Axial  
 T1, T2 coronal T2  
 가  
 VOI(volume of interest)  $1.5 \times 1.0 \times 3.0 \text{ cm}^3$   
 voxel , 가 LCMoel<sup>40)</sup> 2.02 ppm NAA,  
 oblique axial T2 (4,000 msec 3.03 ppm Cr 3.2 ppm Cho  
 TR, 105 msec TE, field of view  $22 \times 22 \text{ cm}$ , slice thickness 5.0 mm, slice gap 0.5 mm) voxel NAA, Cho Cr



**Figure 1.** A : Spectra were acquired simultaneously from  $1.5 \times 1.0 \times 3.0 \text{ cm}$  voxel in the left and right hippocampus. B : Representative  $^1\text{H}$ -magnetic resonance spectrum corresponding to a  $1.5 \times 1.0 \times 3.0 \text{ cm}^3$  voxel in the left hippocampus. NAA : N-acetyl-L-aspartate, Cr : Creatine, Cho : Choline-containing compounds. Magnetic resonance imaging shows the location of voxels defined for spectroscopy measurements and an example of  $^1\text{H}$ -magnetic resonance spectra.

**Table 1.** Demographic and clinical variables of the patients with major depressive disorder and matched control subjects

Variable	MDD (n=14)		Controls (n=12)	
	Mean $\pm$ SD	Median	Mean $\pm$ SD	Median
Age (years)	39.79 $\pm$ 9.70	42.00	39.50 $\pm$ 10.31	41.50
Education (years)	11.50 $\pm$ 3.52	11.5	11.50 $\pm$ 1.73	12.0
HDRS*	30.43 $\pm$ 4.11	30.0	1.33 $\pm$ 1.50	1.50
BDI*	27.79 $\pm$ 9.82	27.50	3.17 $\pm$ 2.66	3.00
Onset age (years)	31.42 $\pm$ 10.22	-	-	-
Duration of illness (months)	93.57 $\pm$ 98.07	-	-	-
Number of episodes	3.00 $\pm$ 1.96	-	-	-
Duration of current episode (months)	8.89 $\pm$ 8.45	-	-	-
Duration of medication (months)	14.00 $\pm$ 20.70	-	-	-
Duration of unmedication (months)	79.57 $\pm$ 82.82	-	-	-

MDD : major depressive disorder, HDRS : Hamilton Depression Rating Scale, BDI : Beck Depression Inventory. \* :  $p < 0.01$  by Mann-Whitney U-test

Mirtazapine 가

6 mirtazapine

) ( (%))

5. 통계분석

NAA/Cr, Cho/Cr, Cho/NAA

(%) =

( - ) \* 100

Mann - Whitney U - test

mirtazapine

p<0.05

SPSS

Wilcoxon signed rank

SPSS 11.0, SPSS Inc., Chicago, Illinois, USA)

test

Mirtazapine

결 과

( metabolites(%))

( HDRS(%),

BDI(%)),

1. 인구학적 특성

Spearman

**Table 2.** Clinical variables and neuropsychological test performance before and after mirtazapine treatment in 14 female patients with major depressive disorder

	Pretreatment (n=14)			Posttreatment (n=14)		
	Mean	SD	Median	Mean	SD	Median
HDRS**	30.43	4.11	30.00	14.79	10.26	13.00
BDI**	27.79	9.82	27.50	16.64	13.85	13.00
WMS-III						
Verbal/Logical Memory						
Immediate*	23.79	10.36	22.00	31.07	11.50	31.50
Delayed*	17.50	10.29	14.50	24.00	10.02	25.00
Visual Memory						
Immediate**	30.07	13.90	28.00	39.57	13.53	39.50
Delayed**	29.79	14.50	28.50	37.86	14.91	37.50
K-AVLT						
Total	45.50	8.67	46.00	48.57	9.07	49.00
Delayed	11.00	2.51	11.00	11.07	2.74	11.50
RCFT						
Immediate**	18.04	6.99	18.25	23.96	7.00	26.75
Delayed**	19.14	5.62	19.50	24.64	6.65	25.50
Color Trail Making						
A	57.21	30.48	50.50	48.00	20.97	44.00
B	122.07	75.12	83.50	103.21	40.28	85.00
IQ	103.93	6.70	103.50	105.14	7.44	105.00

HDRS : Hamilton Depression Rating Scale (17 items), BDI : Beck Depression Inventory, WMS-III : Wechsler Memory Scale-III, K-AVLT : Korean-Auditory Verbal Learning test, RCFT : Rey-Osterrieth Complex Figure Test. \*\* : p<0.01, \* : p<0.05 by Wilcoxon signed rank test

1 . 가 .  
 $31.4 \pm 10.2$   
 $8.9 \pm 8.5$  ,  
 $3.0 \pm 2.0$  .

**2. Mirtazapine 치료가 우울증의 경중도, 신경인지 기능에 미치는 영향**

mirtazapine 가 (HDRS, 30.  $43 \pm 4.11$  vs  $14.79 \pm 10.26$ ,  $p < 0.01$  ; BDI,  $27.79 \pm 9.82$  vs  $16.64 \pm 13.85$ ,  $p < 0.01$  ; 2).

mirtazapine WMS- ( ), RCFT , K - AVLT CTT 가 ( 2).

**3. Mirtazapine 치료가 뇌 대사물질에 미치는 영향**

(NAA/Cr, Cho/Cr, Cho/NAA) 가 . Mirtazapine 가 .

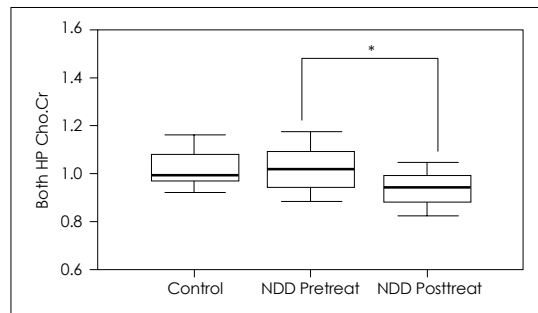
mirtazapine , Cho/Cr ( + Cho/Cr ) ( Cho/Cr,  $1.08 \pm 0.26$  vs Cho/Cr,  $0.95 \pm 0.10$ ,  $Z = -2.09$ ,  $p < 0.05$ ).

NAA/Cr, Cho/NAA mirtazapine 가 ( 3, 2). Cho/Cr(%) BDI (%), HDRS (%) 가 .

**Table 3.** Changes in the ratio of the hippocampal metabolite concentrations before and after mirtazapine treatment in 14 female patients with major depressive disorder

Variable	Pretreatment		Posttreatment	
	Mean $\pm$ SD	Median	Mean $\pm$ SD	Median
Left Hippocampus				
NAA/Cr	$1.80 \pm 0.44$	1.86	$1.63 \pm 0.56$	1.76
Cho/Cr	$0.51 \pm 0.07$	0.51	$0.47 \pm 0.04$	0.46
Cho/NAA	$0.30 \pm 0.09$	0.26	$0.34 \pm 0.17$	0.28
Right Hippocampus				
NAA/Cr	$2.16 \pm 0.76$	1.94	$1.64 \pm 0.54$	1.56
Cho/Cr	$0.54 \pm 0.22$	0.52	$0.48 \pm 0.07$	0.47
Cho/NAA	$0.27 \pm 0.05$	0.28	$0.31 \pm 0.08$	0.30
Both Hippocampus				
NAA/Cr	$3.96 \pm 1.07$	3.64	$3.25 \pm 0.95$	3.06
Cho/Cr*	$1.08 \pm 0.26$	1.02	$0.95 \pm 0.10$	0.94
Cho/NAA	$0.57 \pm 0.14$	0.55	$0.65 \pm 0.21$	0.58

NAA : N-acetyl-L-aspartate, Cr : creatine, Cho : choline-containing compounds. \* :  $p < 0.05$  by Wilcoxon signed rank test



**Figure 2.** Comparison of Cho/Cr ratio in hippocampus (HP) of patients with major depressive disorder (MDD) before and after mirtazapine treatment. Cho : Choline-containing compounds, Cr : creatine, M : Median. \* :  $p < 0.05$ .

## 고 찰

mirtazapine 가 가 mirtazapine 가 가

Mirtazapine 가

1) mirtazapine 가 , 가  
 NAA/Cr 가 ; 2) 가  
 Cho/Cr phosphodiester (PDE) phospholipase  
 ; 3) Cho/Cr A2(PLA2) 가 가 (13,15)  
 가 가  
 NAA/Cr mirtazapine 가  
 , mirtazapine , mirtazapine

가  
 Cho/Cr mirtazapine  
 , HPA axis  
 , mirtazapine 가 (45 - 47)  
 .  
 acetylcholine , 가  
 , (41,42) 가  
 가 (43)  
 mirtazapine 가  
 ,  
 mirtazapine (44) Cho 가 PLA2 (15)  
 가 mirtazapine 가  
 가 가  
 mirtazapine , mirtazapine (50) ECT  
 Cho 83% (20 - 25)  
 PtdCho PCho  
 GPCho . PtdCho mirtazapine 가  
 , acetylcholine 가  
 free choline  
 Cho  
 ,  
 mirtazapine 가 (13,15 - 17)  
 ,  
 PCho GPCho

가 , voxel

NAA voxel 가

HPA axis 가

pine mirtaza- (53,54) 가

가 , 가

결 론

voxel mirtazapine 가

NAA 가

mirtazapine mirtazapine

,<sup>20-25</sup> mirtazapine 가

가 mirtazapine

multi - voxel

Cho 가

Cho 가

PLA2 , PDE phosph- 중심 단어 : mirtazapine .  
homoenoesters <sup>31</sup>P - MRS

Cho (13)

voxel

voxel (51,52)

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