

정신분열병에서 도파민 대사물에 대한 에스트로겐의 영향

전진숙* · 이장현** · 오병훈***

The Influence of Estrogen on Dopamine Metabolites in Schizophrenia

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ABSTRACT

Objectives : The aims of this study were to discriminate the clinical differences, to measure the estrogen and homovanillic acid levels, to evaluate a correlation between estrogen and homovanillic acid, and to identify an association of cognitive deficit with estrogen and homovanillic acid among male and female schizophrenics.

Methods : In addition to the structured interviews, the plasma estrogen levels by radioimmunoassay and the homovanillic acid levels by HPLC were measured in 20 male and 21 female schizophrenics as well as 10 healthy male and 9 female controls.

Results : 1) The plasma estrogen levels were higher in females than males, and significantly higher in female schizophrenics than female controls. The homovanillic acid levels were higher in female schizophrenics than female controls, and were lower in male schizophrenics than male controls.

2) The onset age seemed to be earlier in male schizophrenics, and the frequency of admission, duration of antipsychotic drug administration, dosage of antipsychotics and duration of illnesses were more in males. The estrogen and homovanillic acid levels were significantly higher in female schizophrenics.

3) The estrogen levels had a significant positive correlation with sex, age and onset age, while the homovanillic acid levels did with sex. However, estrogen were not correlated with homovanillic acid levels.

4) The estrogen and homovanillic acid levels were not significantly different between male and female schizophrenics with cognitive deficits. In the schizophrenic patients without cognitive deficits, the estrogen levels were significantly higher in females, while there were no significant sex differences in homovanillic acid.

5) In the male and female schizophrenics predominantly with negative symptoms, there were no significant differences in estrogen and homovanillic acid levels. In those predominantly with positive symptoms, the estrogen levels were significantly higher in females, while there were no sex differences in homovanillic acid levels.

6) In schizophrenics with undifferentiated subtype, the estrogen and homovanillic acid levels were significantly higher in females. In those with paranoid or disorganized subtypes, the estrogen levels were significantly higher in females, while there were no sex differences in the homovanillic acid levels.

7) The mean values of PANSS-negative, PANSS-total, PANSS-CF, MMSE-K and estrogen levels were significantly higher in male schizophrenics with cognitive deficits. The mean values of illness duration, CGI, PANSS-positive, PANSS-negative, PANSS-total, PANSS-CF and MMSE-K were significantly higher in female schizophrenics with cognitive deficits.

8) The variables which showed significant correlation with cognitive deficits were PANSS-negative, PANSS-total, PANSS-CF, MMSE-K and estrogen levels in male schizophrenics. The variables which showed significant correlation with cognitive deficits were subtypes, onset age, illness duration, CGI, PANSS-

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) (051) 250 - 5070, 240 - 6245,) (051) 241 - 5069

positive, PANSS-negative, PANSS-total, PANMSS-CF and MMSE-K in female schizophrenics. The estrogen levels were significantly correlated with admission frequencies, history of antipsychotic administration, duration of antipsychotic administration and cognitive deficits in male schizophrenics, while age were not correlated with in females. The homovanillic acid levels had a significant correlation with subtypes and onset age in male schizophrenics, while there were no correlation among variables in females.

Conclusions : Although the plasma concentrations of estrogen and homovanillic acid in female schizophrenics were significantly higher than males, we could not find an association between them. Furthermore, the various factors affecting on the cognitive deficits, estrogen and homovanillic acid levels seemed to be somewhat different according to sex.

KEY WORDS : Schizophrenia · Estrogen · Dopamine metabolites · Cognitive deficits · Positive symptoms · Undifferentiated type.

서론

Psychiatric Association 1994)

18 45

20

21

18 45

10

9

(Seeman 1982 ; Salokangas 1983).

(Mor -

isette Di Paolo 1993)

31.8 ± 5.8

31.9 ± 2.2

(Seeman Lang 1990),

가

34.6 ±

(Ha -

7.6

32.3 ± 3.0

llonquist 1993 ; Hlfner 1993a).

(1).

2. 연구방법

2

homovanillic acid(HVA)

CGI,

Kay (1987)

Positive and Negative Syndrome Scale(PA -

NSS),

Mini - Mental State Exa -

mination(MMSE - K)(

1989 ;

1989) Positive and Negative Syndrome Scale - Co -

gnitive Function(PANSS - CF)

가

대상 및 방법

1. 연구대상

DSM - (American

Table 1. Comparison of estrogen and homovanillic acid(HVA) levels between controls and schizophrenics

	Males		Females	
	Controls(N=10)	Schizophrenics(N=20)	Controls(N=9)	Schizophrenics(N=21)
Age(Yrs)	31.9 ± 2.2	31.8 ± 5.8	32.3 ± 3.0	34.6 ± 7.6
Estrogen(pg/mL)	64.54 ± 19.65	74.88 ± 37.12	163.00 ± 64.35	167.20 ± 115.84**
HVA(ng/mL)	8.10 ± 2.64	6.48 ± 1.68*	7.27 ± 1.92	10.84 ± 9.33

These data represented mean ± S.D.

*p=0.05 by the t-test

**p=0.004 between schizophrenic males and females by ANOVA with Scheffe's multiple comparison test

1) 에스트로겐 농도측정

4cc (competitive radioimmunoassay method) (double antibody method)

Ethyl acetate : hexane = 3 : 2 가
20
5.0mL glass vial nitrogen
Diluent buffer 5.0mL(2.5mL) vortex

NSB, O, standard(A F), 500 µL 가 (NSB diluent buffer 0.6mL, O diluent buffer 0.5mL 가).
Anti estrogen NSB 100 µL 가 .
¹²⁵I 17 -estradiol 100 µL 가 .
90 incubation . second ant -
ibody 100 µL 가 . 1
incubation . 4 , 1000 × g 15 .
decant 1 - counter
activity .

2) Homovanillic acid 농도측정

5cc (high performance liquid chromatography, HPLC) HVA
(25% PCA) 가 1 , 20 11750g
, 25% 3 가 ,
HPLC
SPSS for Windows, Version 8.0

결 과

1. 남녀 대조군과 정신분열병군에서 Estrogen과 Homovanillic Acid 농도의 비교

HVA
1 (1).
(64.54 ± 19.65pg/mL) (74.88 ± 37.12pg/mL)
64.35pg/mL) (163.00 ± 64.35pg/mL)
(167.20 ± 115.84pg/mL)
(p=0.004).
HVA 8.10 ± 2.64ng/mL,
6.48 ± 1.68ng/mL, 7.27 ± 1.92ng/mL,
10.84 ± 9.33ng/mL
(p=0.05).

2. 남녀 정신분열병군에서 변인의 비교

2 (2).
(p=0.091), (p=0.002), HVA (p=0.046)
가 , , 가 .

3. 정신분열병군에서 Estrogen, Homovanillic Acid 농도와 여러 변인의 연관성

HVA
3 (3).
(= 0.478, p=0.002), (= 0.512,
(= 0.400, p=0.010)
, HVA (=

Table 2. Comparison of variables between schizophrenic males and females

	Schizophrenic males(N=20)	Schizophrenic females(N=21)	p-Value*
Education(Yrs)	12.1 ± 2.7	10.5 ± 3.1	p=0.091
Onset age(Yrs)	23.3 ± 5.5	27.1 ± 7.6	p=0.069
Admission(times)	3.2 ± 2.4	3.1 ± 2.4	p=0.939
Age(Yrs)	31.8 ± 5.8	34.6 ± 7.6	p=0.183
Family history	1.8 ± 0.4	1.8 ± 0.4	p=0.655
Drug history	1.1 ± 0.3	1.2 ± 0.4	p=0.425
Dosage(mg)	682.5 ± 575.0	528.6 ± 482.6	p=0.358
Duration of medication(months)	3.4 ± 2.8	2.9 ± 3.3	p=0.620
Treatment response	1.7 ± 0.9	1.3 ± 0.9	p=0.195
Duration of illness (months)	8.0 ± 3.4	7.0 ± 4.6	p=0.456
CGI ¹	5.2 ± 0.6	5.2 ± 0.8	p=0.683
PANSS ² -positive	24.7 ± 6.3	23.9 ± 3.1	p=0.585
PANSS ² -negative	22.4 ± 5.7	23.4 ± 4.2	p=0.493
PANSS ² -total	94.4 ± 9.3	95.2 ± 11.6	p=0.811
PANSS-CF ³	15.8 ± 2.4	15.9 ± 3.4	p=0.910
MMSE-K ⁴	26.6 ± 2.4	25.5 ± 3.4	p=0.252
Estrogen(pg/mL)	74.88 ± 37.12	167.20 ± 115.84	p=0.002
Homovanillic acid (ng/mL)	6.48 ± 1.68	10.84 ± 9.33	p=0.046

•These data represented mean ± S.D.

*2-tailed t-test

¹Clinical Global Impression

²Positive and Negative Syndrome Scale

³Positive and Negative Syndrome Scale-Cognitive Function

⁴Mini-Mental State Examination-Korean Version

0.313, p=0.046)

HVA

4. 남녀 정신분열병군에서 인지 장애 유무에 따른 Estrogen, Homovanillic Acid 농도의 비교

HVA 4 (4) 가
(MMSE - K 24) 3 (15.0%)
7 (33.3%) , 가 (MMSE -
K 25) 17 (85.0%) 14
(66.7%) 가

HVA 가
가
(p=0.002), HVA
가

5. 남녀 정신분열병군에서 정신 증상에 따른 Estrogen, Homovanillic Acid 농도의 비교

HVA 9%) ,

5 (5).

13 (65.0%)

13 (61.

7 (35.0%)

Table 3. Correlation of estrogen and homovanillic acid levels with variables in schizophrenics

	Estrogen		Homovanillic acid	
	Correlation Coefficients ()	p-Value*	Correlation Coefficients ()	p-Value*
Subtype	-0.071	0.658	0.106	0.509
Sex	0.478	0.002	0.313	0.046
Age	0.512	0.001	0.103	0.523
Education	-0.276	0.080	-0.038	0.812
Onset age	0.400	0.010	0.126	0.433
Admission	0.012	0.939	0.076	0.639
Family history	0.160	0.317	0.092	0.569
Drug history	0.154	0.337	0.069	0.666
Dosage	0.013	0.936	-0.124	0.438
Medication duration	0.046	0.777	-0.026	0.872
Treatment response	-0.088	0.583	-0.208	0.191
Duration of illness	0.187	0.242	-0.048	0.764
CGI ¹	0.127	0.428	-0.087	0.590
PANSS ² -positive	0.116	0.471	0.072	0.653
PANSS ² -negative	0.057	0.723	0.017	0.917
PANSS ² -total	0.063	0.696	0.057	0.725
PANSS-CF ³	0.031	0.849	0.082	0.610
MMSE-K ⁴	-0.188	0.239	-0.021	0.897
Estrogen	1.000		-0.057	0.725
Homovanillic acid	-0.057	0.725	1.000	

*2-tailed t-test

¹Clinical Global Impression

²Positive and Negative Syndrome Scale

³Positive and Negative Syndrome Scale-Cognitive Function

⁴Mini-Mental State Examination-Korean Version

Table 4. Comparison of estrogen and homovanillic acid levels according to the cognitive deficits in schizophrenics

Cognitive deficits	Estrogen (pg/mL)	Homovanillic acid (ng/mL)
Yes(MMSE-K 24)		
Males(N=3, 15.0%)	113.67 ± 51.76	7.23 ± 1.76
Females(N=7, 33.3%)	200.44 ± 165.13	11.30 ± 4.68
p-Value*	p=0.412	p=0.193
No(MMSE-K 25)		
Males(N=17, 85.0%)	70.46 ± 31.14	6.07 ± 1.11
Females(N=14, 66.7%)	153.62 ± 87.31	11.05 ± 11.45
p-Value*	p=0.002	p=0.104

•These data represented mean ± S.D.

*2-tailed t-test

•Statistically non-significant between males with and without cognitive deficits in estrogen(p=0.064) and homovanillic acid(p=0.146) levels

•Statistically non-significant between females with and without cognitive deficits in estrogen(p=0.413) and homovanillic acid (p=0.958) levels

Table 5. Comparison of estrogen and homovanillic acid levels according to the psychiatric symptoms in schizophrenics

Psychiatric symptoms	Estrogen (pg/mL)	Homovanillic acid (ng/mL)
Positive symptoms		
Males(N=13, 65.0%)	67.58 ± 29.12	6.27 ± 1.39
Females(N=13, 61.9%)	202.74 ± 127.39	12.73 ± 11.94
p-Value*	p=0.002	p=0.076
Negative symptoms		
Males(N=7, 35.0%)	97.82 ± 46.08	6.25 ± 1.04
Females(N=8, 38.1%)	120.91 ± 88.17	8.75 ± 2.89
p-Value*	p=0.572	p=0.068

- These data represented mean ± S.D.
- *2-tailed t-test
- Statistically non-significant between males with positive and negative symptoms in estrogen(p=0.106) and homovanillic acid (p=0.980) levels
- Statistically non-significant between females with positive and negative symptoms in estrogen(p=0.132) and homovanillic acid (p=0.371) levels

Table 6. Comparison of estrogen and homovanillic acid levels according to the subtypes in schizophrenics

Subtypes	Estrogen (pg/mL)	Homovanillic acid (ng/mL)
Undifferentiated		
Males(N=12, 60.0%)	84.52 ± 42.60	5.89 ± 1.10
Females(N=9, 42.9%)	195.79 ± 150.97	11.28 ± 4.82
p-Value*	p=0.031	p=0.002
Negative symptoms		
Males(N=8, 40.0%)	66.89 ± 26.18	6.84 ± 1.34
Females(N=12, 57.1%)	148.92 ± 84.77	11.03 ± 12.32
p-Value*	p=0.026	p=0.389

- These data represented mean ± S.D.
- *2-tailed t-test
- Statistically non-significant between males with undifferentiated and paranoid/disorganized subtypes in estrogen(p=0.343) and homovanillic acid(p=0.119) levels
- Statistically non-significant between females with undifferentiated and paranoid/disorganized subtypes in estrogen(p=0.392) and homovanillic acid(p=0.955) levels

8 (38.1%)

HVA

가

가

(p=0.002), HVA

가

가

가

6. 남녀 정신분열병군에서 아형에 따른 Estrogen, Homovanillic Acid 농도의 비교

HVA

6 (6).

12 (60.0%)

9 (42.9%)

8 (40.0%)

12

(57.1%)

(p=0.031)

HVA

(p=0.002)가

가

(p=0.026), HVA

가

가

가

7. 남녀 정신분열병군에서 인지 장애 유무에 따른 여러 변인의 비교

7 (7).

가 PANSS

(p<0.05), PANSS

(p<0.05), PANSS - CF

(p<0.01), MMSE - K

(p<0.001),

(p<0.05)가

가

(p<0.05), CGI (p<0.001), PANSS (p<0.001), PANSS (p<0.001), PANSS - CF (p<0.001), MMSE - K (p<0.001)

가

가

가

8. 남녀 정신분열병군에서 인지 장애, Estrogen 및 Homovanillic Acid 농도와 여러 변인의 연관성

HVA

8 (8).

PANSS

, PANSS

, PANSS - CF

, MMSE - K

, CGI, PANSS

PANSS

, PANSS

, PANSS - CF

MMSE - K

고찰

. HVA

, 가

Table 7. Comparison of variables between schizophrenic males and females according to cognitive deficit

	Schizophrenic males(N=20)		Schizophrenic females(N=21)	
	MMES	K 24(N=3)	MMES	K 24(N=3)
Type	1.3 ± 0.6	1.4 ± 0.5	1.1 ± 0.4	1.7 ± 0.5*
Sex	1.0 ± 0.0	1.0 ± 0.0	2.0 ± 0.0	2.0 ± 0.0
Education(Yrs)	13.3 ± 2.3	11.8 ± 2.8	10.0 ± 2.4	10.7 ± 3.4
Onset age(Yrs)	28.0 ± 5.0	22.4 ± 5.2	22.0 ± 7.6*	29.7 ± 6.4
Admission(times)	2.3 ± 2.5	3.4 ± 2.4	3.9 ± 2.2	2.8 ± 2.5
Age(Yrs)	37.0 ± 6.1	30.8 ± 5.4	32.7 ± 8.3	35.6 ± 7.3
Family history	1.7 ± 0.6	1.8 ± 0.4	1.7 ± 0.5	1.9 ± 0.4
Drug history	1.3 ± 0.6	1.1 ± 0.2	1.1 ± 0.4	1.2 ± 0.4
Dosage(mg)	516.7 ± 448.1	711.8 ± 601.2	507.1 ± 493.7	539.3 ± 495.4
Medication duration(Ms)	1.7 ± 1.4	3.7 ± 2.9	4.0 ± 2.3	2.3 ± 3.7
Treatment response	1.7 ± 1.5	1.7 ± 0.8	1.6 ± 0.8	1.2 ± 0.9
Duration of illness(Ms)	8.6 ± 2.7	7.8 ± 3.6	10.3 ± 4.2*	5.4 ± 3.9
CGI ¹	5.7 ± 1.2	5.1 ± 0.4	6.0 ± 0.6***	4.9 ± 0.5
PANSS ² -positive	25.7 ± 7.4	24.5 ± 6.3	25.9 ± 4.0*	22.9 ± 1.9
PANSS-negative	29.0 ± 2.6*	21.2 ± 5.3	28.0 ± 3.7***	21.1 ± 2.0
PANSS-total	105.7 ± 14.6*	92.4 ± 6.9	106.7 ± 13.6***	89.4 ± 3.8
PANSS-CF ³	19.0 ± 3.6**	15.2 ± 1.7	19.3 ± 3.4***	14.2 ± 1.7
MMSE-K ⁴	21.7 ± 2.1***	27.5 ± 1.1	21.9 ± 3.0***	27.4 ± 1.6
Estrogen(pg/mL)	113.67 ± 51.76*	68.03 ± 31.13	200.44 ± 165.13	150.58 ± 84.66
Homovanillic acid(ng/mL)	7.23 ± 1.76	6.35 ± 1.69	11.30 ± 4.68	10.61 ± 11.12

*p<0.05, **p<0.01, ***p<0.001

¹Clinical Global Impression³Positive and Negative Syndrome Scale-Cognitive Function

•These data represented mean ± S.D.

²Positive and Negative Syndrome Scale⁴Mini-Mental State Examination-Korean Version**Table 8.** Correlation of cognitive deficit, estrogen and homovanillic acid(HVA) levels with variables in schizophrenic males and females

	Schizophrenic males(N=20)			Schizophrenic females(N=21)		
	Cognitive deficit	Estrogen	HVA	Cognitive deficit	Estrogen	HVA
Type	0.057	-0.160	0.470*	0.539*	-0.170	0.021
Age	-0.389	-0.175	0.280	0.182	0.667**	0.013
Education	-0.202	0.147	-0.144	0.113	-0.285	0.089
Onset age	-0.375	-0.044	0.276	0.488*	0.408	0.015
Admission	0.159	-0.460*	-0.063	-0.216	0.168	0.128
Family history	0.081	-0.035	-0.120	0.171	0.233	0.131
Drug history	-0.327	0.568*	0.035*	0.086	0.007	0.035
Dosage	0.124	-0.233	-0.166	0.032	0.239	-0.096
Medication duration	0.260	-0.517*	-0.102	-0.249	0.264	0.014
Treatment response	0.016	-0.151	0.138	-0.201	0.068	-0.253
Duration of illness	-0.083	-0.255	0.081	-0.518*	0.421	-0.025
CGI ¹	-0.379	0.047	0.344	-0.718**	0.132	-0.188
PANSS ² -positive	-0.066	0.201	0.240	-0.474*	0.297	0.156
PANSS-negative	-0.502*	0.092	0.156	-0.791**	-0.029	-0.068
PANSS-total	-0.525*	0.178	0.404	-0.719**	0.024	0.005
PANSS-CF ³	-0.575**	0.272	0.359	-0.729**	-0.027	0.056
MMSE-K ⁴	0.873**	-0.407	-0.335	0.785**	-0.060	0.090
Cognitive deficit	1.000	-0.450*	-0.193	1.000	-0.208	-0.036
Estrogen	-0.450*	1.000	0.232	-0.208	1.000	-0.276
Homovanillic acid	-0.193	0.232	1.000	-0.036	-0.276	1.000

*p<0.05, **p<0.01

¹Clinical Global Impression³Positive and Negative Syndrome Scale-Cognitive Function

•These data represented correlation coefficients()

²Positive and Negative Syndrome Scale⁴Mini-Mental State Examination-Korean Version

가 , 가 (1998) 8 가

가 (Gold 1998).

(1998) PA -

Cole(1997) . Jablensky 8

NSS, CGI 가 . Morissette Di Paolo(1993) 가

. Murthy (1998) 가

(Di

, D₂ Paolo 1982). Hlfner (1993b)

가 3.2 4.1 가 , 45 54

가

, D₂ 가 ,

(Salokangas 1983). D₂ . Hlfner (1998)

, 40 . Hlfner D₂

가 , 가 , serotonin glut -

Mayer (1993) amate

(apathetic), 가

가 HVA 가 ,

. Meltzer (1997) 가

가 Sumiyoshi (1997)

HVA 가 ,

prolactin(PRL) .

HVA가 가 DA turnover (renal clearance)

D₂ 가

가 D₂ 가 가 ,

가 (Riecher - R=ssler Hlfner 1993 ; 가 가 ,

Seeman 1997). Kulkarni (1996) (Po -

8 0.02mg estradiol hjalainen 1998).

estradiol , (prefrontal)

. Hietala (1994) (st -

riatal) D₂ . Davis 가 (Zukin Javitt (1991) 1991). (1999) TD가 HVA 가 가 , glutamate dehydrogenase , 가 . Swerdlow (1997) HVA 가 , prepulse inhibition(PPI) 가 (Csernansky Newcomer , PPI est - 1994). rogen progesterone (midluteal) , (sulcal) , (temp - oral horn) , (hippocampus) , (corpus callosum) . Nopoulos (1997) (executive) , (sustained attention), 가 Goldstein (1998) .

가 , HVA 가 .

가 , 가 ,

가 , Hoff (1998) (Scu - lly 1997). Hoff (1998) (visual memory) 가 Rupniak Iversen (1993) noradrenaline , 결론 HVA apomorphine D₁ D₂ 가 , HVA catecholamine . Servan - Schreiber (1998) , Wade (1993) 20 21 , (tardive dyskinesia, TD) 10 9 , Goldberg Geld(1995) HVA 1) 가 TD , HVA (Meltzer 1994). 5 - HT_{2A} D₄ serotonin 가 glutamate .

2) 가
 ,
 가 HVA

3) ,
 , HVA
 HVA

4) 가 HVA
 가
 가
 가 , HVA

5) HVA
 가
 , HVA

6) HVA 가
 , HVA 가

7) 가 PANSS
 , PANSS , PANSS - CF, MMSE - K,
 가 가
 , CGI, PANSS , PANSS
 , PANSS , PANSS - CF, MMSE - K가
 가

8) PANSS , PANSS , PANSS - CF, MM -
 SE - K,
 , CGI, PANSS
 , PANSS , PANSS , PANSS - CF, MMSE -
 K
 가 HVA
 HVA
 HVA
 가

중심 단어 :

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