

Lithium에 의한 양극성 기분장애환자의 임파구 Inositol Monophosphatase mRNA 양의 변화와 임상경과

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The Relationship between Change of Lymphocyte Inositol Monophosphatase mRNA Level by Lithium and Clinical Course in Bipolar Affective Disorder

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ABSTRACT

Objective : Lithium inhibits the action of inositol monophosphatase(IMPase) in phosphoinositide(PI) signal transduction system at therapeutically relevant concentration. The depletion of inositol by lithium itself cannot explain the lithium's therapeutic effect. However, attention has focused on the abnormality of PI signal transduction system as the pathophysiology of bipolar affective disorder(BPD). We investigated whether IMPase mRNA levels of lymphocytes would be different between BPD patients(n=16) and age, sex - matched normal controls(n=16). We also investigated the change of IMPase mRNA level by lithium during 4 weeks to probe the possibility that IMPase mRNA levels could predict the therapeutic response to lithium and clinical course.

Method : Relative IMPase mRNA levels in lymphocyte were quantified by reverse transcriptase(RT) - PCR in sixteen drug - free BPD patients and sex, age - matched normal controls. The psychopathology of patients were measured using YMRS (Young Mania Rating Scale) and CGI(Clinical Global Impression).

Results : There was no significant difference in IMPase mRNA levels between BPD patients and normal controls. And the IMPase mRNA levels were not significantly changed by 4 week treatment with lithium. However, the basal IMPase mRNA levels were negatively correlated with the changes of CGI after 4 weeks. Furthermore, the patients with relatively high basal IMPase mRNA levels showed much more improvement during 4 weeks.

Conclusions : BPD patients and normal controls were not distinguished by lymphocyte IMPase mRNA level. Although we do not support the hypothesis that lymphocyte IMPase activity would be related with the pathogenesis of BPD and the action of lithium, these data raise the possibility that lymphocyte IMPase mRNA levels could function as a predictor of therapeutic response and clinical course of BPD.

KEY WORDS : Lithium · Inositol monophosphatase mRNA · Bipolar affective disorder · Lymphocyte.

서
론

1949 John Cade
lithium

(Cade

1949),
가

Lithium

. Lithium

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가 IMPase lithium 가

lithium IMPase mRNA , IMP-

2 (signal trans- ase mRNA

duction system) (Bourne 가

Nicoll 1993 ; Manji 1992 ; Manji 1995).

2 IMPase mRNA lithium

phosphoinositide(PI) PI (basal level) 가

, lithium inositol monophosphatase , IMPase mRNA

(IMPase) inositol phos- lithium IMPase mRNA

phate가 inositol 가

phosphatidylinositol 4,5 - bisphosphate(PIP₂)

(Baraban 1994 ; Hallcher Sherman

1980 ; Pollack 1994).

lithium 가 IMPase

inositol (Berridge

1982 ; Berridge 1984 ; Hallcher Sherman 1980).

lithium 가 ,

가

lithium 가 inositol 20

(Alan 1997).

PI

가 2

PI

20 , ,

(Brown 1993 ; Friedman 1993 ; Jope 1996 ;

Jope Williams 1994 ; Shamir 1998).

PI

가

가

lymphoblastoid cell line , Young

IMPase Mania Rating Scale(YMRS, Young 1978), Clinical

가 lithium (Shamir 1998) .

IMPase , YMRS, CGI 가 4

IMPase mRNA ,

IMPase mRNA YMRS 11 , CGI

lithium IMPase mRNA , 가 1

가 (Nemanov 1999).

IMPase Pearson 0.896(p<.01) .

연구대상 및 방법

1. 연구대상

1999 11 2000 6

4 (DSM - , APA 1994)

2. 정신병리의 평가 및 약물사용 방법

1) 정신병리의 평가

, Young

Mania Rating Scale(YMRS, Young 1978), Clinical

Global Impression(CGI, Bech 1993)

가 4

, YMRS, CGI 가

YMRS 11 , CGI

가 가 1

가

Pearson 0.896(p<.01) .

2) 약물사용 방법

lithium
 peridone 600mg, 2 7 900mg
 0.8 1.2mEq/L
 Risperidone 1mg
 1mg , 7
 가

3. IMPase mRNA 측정을 위한 채혈

lithium 10ml
 EDTA , IMPase mRNA
 (basal level) . Lithium 4
 IMPase mRNA
 , IMPase mRNA

4. IMPase mRNA 측정 방법

1) 임파구 세포 준비

10ml EDTA tube , 0.9% NaCl
 2 9ml 4.5ml Lym-
 phoprep™ (Nycomed Pharma, Norway)
 23 , 800 × g 20
 0.9% NaCl 250 × g
 1

2) Total RNA의 분리

TRIZOL reagent(GIBCO BRL, USA)
 total RNA . 50 μl 200 μl
 0.9% NaCl 가 750 μl TRIZOL reagent
 5 , 250 μl Chloroform
 가 5 . 4 , 800 × g 15
 Isopropanol
 1 - 20 RNA . 800 × g 10
 pellet , 70% DEPC alcohol
 . RNA pellet air - dry 0.1% diethyl-
 pyro - carbonate - treated water . RNA
 260nm

3) 역전사(Reverse transcription)

First strand cDNA synthesis SuperScript reverse
 transcriptase assay(GIBCO BRL, USA) . 1 μg
 total RNA, 1 μg Oligo(dT)₁₅ primers(Promega, USA)
 70 10 (denaturation) , 5

first strand buffer(20mM Tris - HCl buffer,
 pH 8.4, 50mM KCl, 2.5mM MgCl₂, GIBCO BRL, USA),
 10mM dithiothreitol, 10U RNasin(Promega, USA), 0.5
 mM dNTPs, 200U SuperScript (Reverse
 transcriptase) 20 μl 42
 1 . Transcriptase
 70 15 가 - 20 .

4) PCR amplification에 사용된 oligonucleotide 시발체(Primer)

Internal standard - actin , IMPase
 PCR oligonucleotide

IMP F : 5 ' - TCCATCTCACAGTTTCAT - 3 ' .

IMP R : 5 ' - CATCTTGCCTTCCACACA - 3 ' .

- actin F : 5 ' - AAGAGAGGCATCCTCACCCCT - 3 ' .

- actin R : 5 ' - TACATGGCTGGGGTGTGAA - 3 ' .

5) Polymerase chain reaction

3 μl 10 × Taq buffer(500mM KCl, 100mM Tris - HCl,
 PH 8.3, 15mM MgCl₂), 2.5 μl 2.5mM dNTPs, 10pmol 5 ' 3 ' primer 1 μl, 1.5U Taq polymerase(Takara, Japan)
 30 μl . PCR
 DNA thermal cycler(HyBaid, UK) 36 cycle
 (denaturation step) 94
 5 , cycle 94 30 , 54
 60 annealing, 72 30 extension
 72 10 extension
 4 .

6) 전기영동 및 분석

5 μl RT - PCR product Tris - borate/EDTA buffer
 2% agarose gel . GelDoc2000 Gel
 Documentation System(Bio - Rad Lab, USA)

5. 통계분석

IMPase mRNA T
 , IMPase mRNA
 IMPase
 mRNA [(,) × (,)]
 . IMPase mRNA ,
 T . SPSS for Windows
 version 8.0 .

연구 결과

1. 인구사회학적 특성

20 가 , 4
 16 (6 , 10)
 가 1 ,
 lithium, risperidone
 가 1 , 가 가 2 .
 31.63 ± 12.26 ,
 (6 , 10) 31.50 ± 12.07 .
 1 .

2. Standard curve

IMPase cDNA - actin cDNA PCR
 1 . Standard
 curve 2 .

3. PCR data 및 relative gene expression의 계산

Internal standard gene gene target
 gene internal standard gene linear amplification
 PCR product .

Ratio of PCR products =

density target gene/density internal standard gene

× volume of internal standard gene/volume of target gene

cDNA target
 gene internal standard gene PCR product
 , primer
 DNA segment PCR
 (empirical) .

Image Analyser GelDoc2000(Bio - Rad Lab,
 USA) . Area gel UV
 PCR product (mm²) intensity(int)
 PCR product . PCR product (vo-
 lume) (area) (intensity) .

Table 1. Demographic data of subjects

	Male	Female
Number	6	10
Age(Mean ± SD)	33.7 ± 15.7	30.4 ± 10.5
Education		
Primary		2
Middle		2
High	3	4
College	3	2
Marital status		
Married	3	5
Single	3	5
Family history of BAD ^a		
Yes		1
No	6	9
Past history of BAD ^a		
Yes	4	7
No	2	3

a : bipolar affective disorder

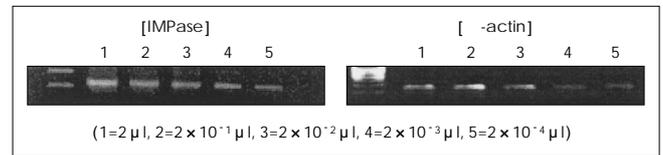


Fig. 1. Quantitative analysis of PCR product after amplification of IMPase and -actin mRNA. PCR was performed on serial 1 : 10 dilution of the reverse transcription product. 1 - 5 lanes of IMPase and -actin showed serially 1 : 10 dilution concentration.

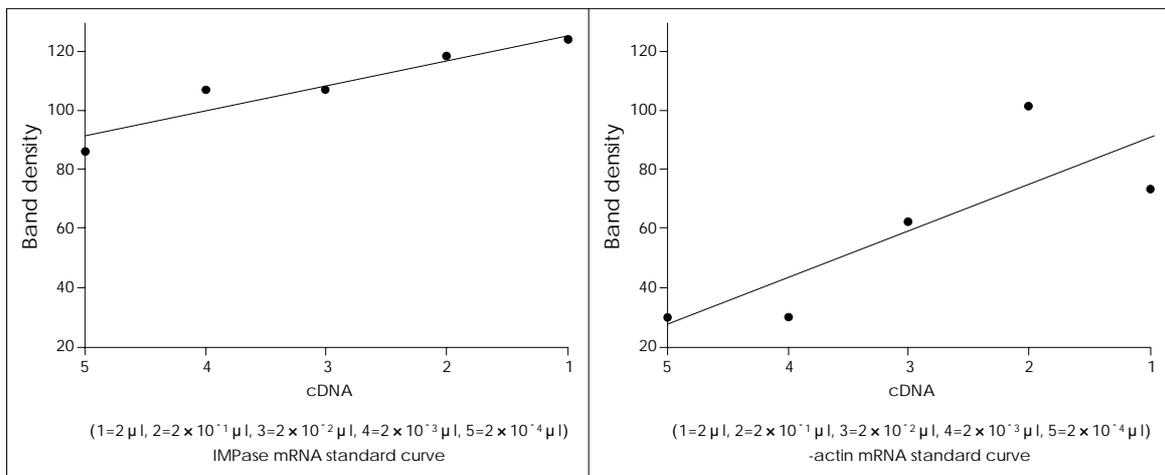


Fig. 2. Standard curve of IMPase mRNA and -actin mRNA.

1) 정상 대조군

IMPase mRNA - actin mRNA PCR product
 0.31 ± 0.12 (2).
 IMPase mRNA

2) 환자군-기초량

IMPase mRNA - actin mRNA PCR product
 NA 0.38 ± 0.25 (3).
 IMPase mRNA

Table 2. IMPase mRNA level of normal control

	IMPase			-actin			IMPase mRNA level
	Area ^a	Volume ^b	Int ^c	Area ^a	Volume ^b	Int ^c	
1	1.40	98.40	70.29	2.97	353.19	118.92	0.27
2	2.15	78.88	36.69	2.97	398.36	134.13	0.19
3	1.98	123.50	62.40	3.92	405.60	103.47	0.30
4	1.32	40.88	30.97	3.14	369.23	117.59	0.11
5	2.60	224.38	86.30	4.33	719.94	166.27	0.31
6	2.48	176.50	71.17	4.53	798.36	176.24	0.22
7	1.98	119.17	60.19	2.23	217.13	97.37	0.54
8	1.61	122.02	75.79	3.14	425.87	135.63	0.28
9	2.48	191.90	77.38	3.92	689.05	175.78	0.28
10	2.10	100.50	47.86	2.35	195.59	83.23	0.51
11	2.10	96.97	46.18	3.14	338.74	107.88	0.28
12	1.73	100.06	57.84	2.97	329.69	111.01	0.30
13	1.98	82.32	41.58	3.14	254.84	81.16	0.32
14	1.07	67.49	63.08	3.14	238.10	75.83	0.28
15	2.23	112.70	50.54	2.35	209.64	89.21	0.54
16	1.61	121.03	75.18	3.30	391.05	118.50	0.30

a : Area=mm² b : Volume=mm² × Intensity c : Int=Intensity

Table 3. IMPase mRNA level of patient group at admission

	IMPase			-actin			IMPase mRNA level
	Area ^a	Volume ^b	Int ^c	Area ^a	Volume ^b	Int ^c	
1	2.10	9.47	4.51	4.70	233.92	49.77	0.04
2	3.14	166.80	53.12	4.33	395.37	91.31	0.42
3	2.23	32.54	14.59	3.30	259.02	78.49	0.13
4	2.48	189.92	76.58	4.13	329.00	79.66	0.58
5	2.35	36.50	15.53	4.70	286.23	60.90	0.13
6	2.48	134.91	54.40	4.70	309.82	65.92	0.44
7	3.30	278.85	84.50	3.47	385.31	111.04	0.72
8	2.23	81.06	36.35	3.30	316.70	95.97	0.26
9	2.97	174.52	58.76	3.14	231.04	73.58	0.76
10	2.23	79.03	35.44	3.92	361.97	92.34	0.22
11	2.31	104.90	45.41	3.30	334.65	101.41	0.31
12	2.35	108.05	45.98	3.14	268.63	85.55	0.40
13	1.57	39.78	25.34	4.13	234.87	56.87	0.17
14	2.23	206.77	92.72	4.70	336.80	71.66	0.61
15	2.10	209.83	99.92	3.30	270.60	82.00	0.78
16	1.98	27.68	13.98	3.92	359.90	91.81	0.08

a : Area=mm² b : Volume=mm² × Intensity c : Int=Intensity

3) 환자군-4주 후

Lithium 4 IMPase mRNA
 - actin mRNA PCR product 4
 IMPase mRNA 0.27 ± 0.14 (4).

5. IMPase mRNA 양 분석(3)

1) 정상 대조군과 환자군의 IMPase mRNA 기초량 비교

IMPase mRNA 가
 IMPase mRNA
 (t=.922, df=21.464, p=.367).

2) 환자군의 IMPase mRNA 기초량과 4주 후 양 비교

IMPase mRNA lithium 4
 IMPase mRNA (t=1.352, df=15, p=.196).

Table 4. IMPase mRNA level of patient group at 4 weeks after admission

	IMPase			-actin			IMPase mRNA level
	Area ^a	Volume ^b	Int ^c	Area ^a	Volume ^b	Int ^c	
1	2.23	201.19	90.22	4.13	609.05	147.47	0.33
2	2.31	128.46	55.61	4.13	562.63	136.23	0.23
3	2.23	58.11	26.06	3.71	525.71	141.70	0.11
4	2.35	62.67	26.67	4.13	645.06	156.19	0.10
5	2.35	198.22	84.35	3.72	556.85	149.69	0.36
6	3.14	258.11	82.20	3.92	600.35	153.15	0.43
7	2.60	48.41	18.62	4.13	506.42	122.62	0.10
8	2.23	99.12	44.45	3.71	422.31	113.83	0.23
9	2.61	64.91	24.87	4.13	470.12	113.83	0.14
10	2.35	92.31	39.28	4.13	459.05	111.15	0.20
11	2.23	200.66	89.98	3.30	411.77	124.78	0.49
12	2.35	49.23	20.95	3.92	465.93	118.86	0.11
13	2.23	106.62	47.81	3.14	406.79	129.55	0.26
14	2.35	182.38	77.61	3.14	408.45	130.08	0.45
15	2.81	253.60	90.25	3.47	592.60	170.78	0.43
16	2.97	160.08	53.90	3.92	369.26	94.20	0.43

a : Area=mm² b : Volume=mm² × Intensity c : Int=Intensity

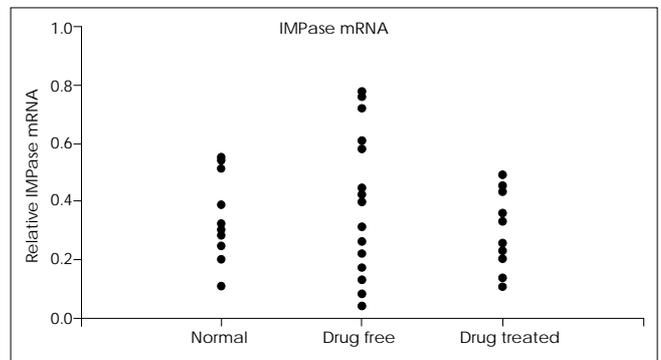


Fig. 3. Comparison of IMPase mRNA level between normal control and patient group.

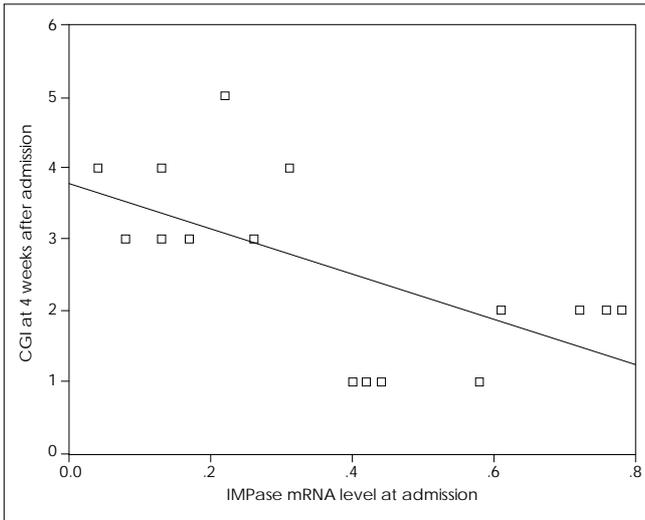


Fig. 4. Correlation between IMPase mRNA level at admission and CGI at 4 weeks after admission.

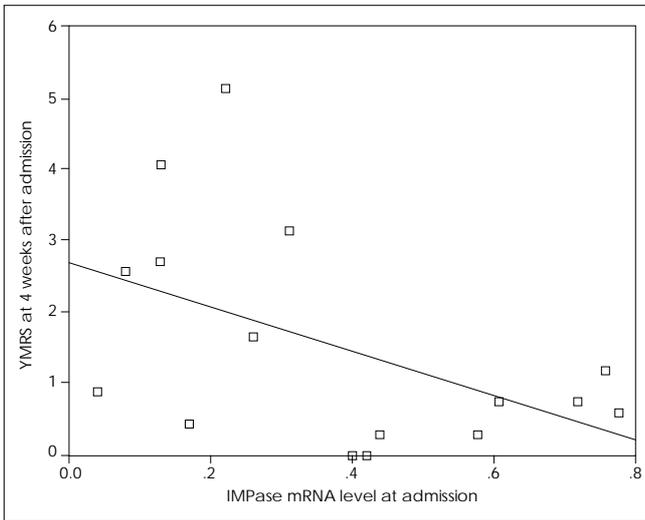


Fig. 5. Correlation between IMPase mRNA level at admission and YMRS at 4 weeks after admission.

6. IMPase mRNA 양과 정신병리 및 임상경과와의 상관관계 분석

IMPase mRNA 4 CGI (r = -.630, p=.009)
 mRNA 4 가 (4).
 IMPase mRNA 4 YMRS (r = -.477, p=.072)(5).

7. IMPase mRNA 양에 대한 성별과 집단의 상호작용 분석

IMPase mRNA (t = -3.154, p=.007)
 4 (p=.029)
 (5).

Table 5. Sex differences of IMPase mRNA level in patient group

	Sex	N	Mean	SD	t	df	Sig. (2-tailed)
IMP0 ^a	Male	6	0.177	0.140	-3.154	14	.007
	Female	10	0.499	0.224			
IMP4 ^b	Male	6	0.282	0.114	.143	14	.888
	Female	10	0.271	0.162			
IMP0-4 ^c	Male	6	-0.105	0.215	-2.434	14	.029
	Female	10	0.228	0.289			

a : IMPase mRNA level at admission
 b : IMPase mRNA level at 4 weeks after admission
 c : change of IMPase mRNA level during 4 weeks

Table 6. Comparison of IMPase mRNA level subgroup

	Sex	N	Mean	SD	t	df	Sig. (2-tailed)
CGIS4 ^a	Low	5	3.400	.548	5.060	8	.001
	High	5	1.800	.447			
CGIS0-4 ^b	Low	5	1.600	1.140	-2.058	7	.079
	High	4	3.000	.817			

a : clinical global impression-severity of illness at 4 weeks after admission
 b : change of clinical global impression-severity of illness during 4 weeks

mRNA 가
 IMPase mRNA IMPase mRNA
 [F(1, 28)=4.754, p=.038]
 [F(1, 28)=10.411, p=.003]

8. 환자군의 IMPase mRNA 기초량 상, 하위집단 사이의 정신병리 및 임상경과 비교

IMPase mRNA 30 percentile
 (IMPase mRNA 0.175,)
 30 percentile(IMPase mRNA 0.566,)
 (6). 4 CGI (3.400 ± 5.48) (1.800 ± .447)
 가 (t=5.060, p=.001). 4 CGI (3.000 ± .817) (1.600 ± 1.140)
 , 4 (t = -2.058, p=.079).

9. 4주 후의 IMPase mRNA 양과 혈중 lithium 농도와의 상관관계

4 IMPase mRNA 2 lithium (r = -.519, p=.047).
 IMPase

고 찰

inositol , IMPase 가
 , IMPase mRNA 가
 Lithium 가 IMPase inositol 가
 inositol 가 (inositol depletion hypothesis)
 (Dixon 1992 ; Hokin 1993 ; Lee 1992)
 (Stubbs Agranof 1993) inositol
 가 , lithium
 inositol triphosphate 가 (Agam 1993),
 (Gur 1996),
 lithium 가 inositol
 (Agam 1993) 가 IMPase가
 lithium inositol , lithium
 (Moore 1999)가 , inositol (Agam Livine 1989 ; Moscovich
 가 1990 ; Shamir 1998). , lithium
 2 IMPase가 lithium lithium
 inositol 가 lithium IMPase IMPase mRNA
 가 가 (Jope
 Williams 1994 ; Manji 1995). IMPase mRNA lithium
 Inositol 가 Shamir
 가 (1998) Nemanov (1999)
 가 PI Shamir (1998) lymphoblastoid cell line IMPase
 , Nemanov (1999) IMPase
 , PIP₂, protein kinase C , mRNA
 inositol phosphate Ca²⁺ , Nemanov
 가 (Brown 1993 ; (1999)
 Dubovsky 1992 ; Friedman 1993 ; Kusumi 1991 ; lithium IMPase
 Mikuni 1991 ; Soares 1999 ; van Calker 1993). mRNA
 Inositol 가 inositol , IMPase 가
 가
 IMPase 가 Lithium 4 IMPase mRNA
 (Atack 1996 ; Shimon 1997), Nemanov (1999)
 inositol 가 (Shimon 4 lithium 가
 1997). lymphoblastoid IMPase mRNA
 IMPase (Shamir lithium 5 inositol
 1998), IMPase mRNA 가 (Moore 1999), lithium
 (Nemanov 1999) 2
 , lithium IMPase
 inositol , inositol IMPase mRNA 가
 IMPase , IMPase 가
 lithium , lithium
 , PI 2

phospholipase C gamma - 1 isozyme
PLCG1 lithium

lithium 가
lithium IMPase mRNA
(Turecki 1998). lithium Nemanov (1999) lithium
inositol polyphosphate 1 - phosphatase lithium IMPase mRNA
enzyme INPP1 gene (C973A tra-
nsversion) 가 (Steen 1998)
lithium IMPase mRNA
lithium IMPase
lithium lymphoblastoid
IMPase (Shamir 1998)
IMPase PI IMPase
가 PI IMPase
(state - dependent) 가
soluble interleukin - 2 receptor(sIL - 2R) 1997), lymphoblastoid IMPase
(Tsai 1999) 가 (Shamir 1998),
creatine 가 IMPase mRNA (Nemanov
(Hamakawa 1999) 가 PI IMPase
IMPase mRNA 가 IMPase
가 IMPase mRNA lithium IMPase IMPase
30 percentile(IMPase mRNA 0.175, IMPase mRNA 가 IMPase
) 30 percentile(IMPase mRNA Lithium inositol
0.566,) 4 lithium 5 ,
가 , inositol
4 Moore (1999)
lithium lithium
IMPase mRNA 가 lithium
, lithium SH - SY5Y activator protein(Ap - 1)
IMPase mRNA IMPase mRNA transcription factor 12 - o - tetradecanoyl - phorbol
Nemanov (1999) lithium 13 - acetate(TPA) response element(TRE) basal sti-
lithium 가 mulated DNA binding 가
IMPase mRNA 가 (Asghari 1998 ; Jope 1999 ; Ozaki Chuang 1997 ;
, 가 Unlap Jope 1997 ; Williams Jope 1995 ; Yuan 1998)
Nemanov (1999) lithium lithium Ap - 1 transcription factor pathway
IMPase mRNA 가 (Hendrick
4 IMPase mRNA 2000 ; Yuan 1998).
IMPase mRNA lithium IMPase mRNA
lithium Nemanov (1999) 가 lithium 가
lithium IMPase mRNA 가
IMPase mRNA 가

(Hendrick 2000 ; Robb 1998).
T Ca²⁺ 가 , IMPase mRNA
(Emam-
ghoreishi 1997) 가 creatine lithium IMPase
가 mRNA
(Hamakawa 가
1999) IMPase mRNA 4
중심 단어 : Inositol monophosphatase mRNA
가
3
가 IMPase mRNA
4 가
가
2 가 ,
가가
요 약
IMPase mRNA lithium
lithium 4
IMPase mRNA 가
, IMPase mRNA
2 lithium 16 ()
6 , 10)
IMPase mRNA RT -
PCR Young Ma-
nia Rating Scale Clinical Global Impression
4
IMPase mRNA
, lithium 4
IMPase mRNA
lithium IMPase
mRNA 4 가
lithium IMPase mRNA

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