[11:50 – 12:20]

The anti-dementia effects of herbal medicine fomula YMJ From lab to clinic

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The herbal extract YMJ has been widely used as an anti-aging herbal medicine for centuries in Asian countries. Among the various modified subscriptions of YMJ, YMJd was formulated to enhance memory retention. This study has three goals: 1) to quantitatively evaluate the memory-enhancing effect of YMJd using behavior tasks; 2) use cDNA micro-array tools to identify candidate genes responsible for enhancing memory; and 3) to evaluate enhancing cognitive ability in normal human subjects and discusses its possibility to be used to treat dementia patients with deficient cognitive ability. Memory retention abilities are addressed by the passive avoidance task with SD male rat. The retention time of the YMJd group was significantly delayed (~100%), whereas *Ginkgo biloba* and Soya lecithin treatment were only delayed 20% and 10%, respectively. In order to confirm the anti-dementia effects of YMJd, ibotenic lesioned alzeheimer's disease model was utilized. Ibotenic lesion of the medial septum (MS) of rat showed the impaired performance in the Morris water maze test and severe cell losses in the MS, as indicated by decreased choline acetyltransferase-immunoreactivity in the medial septum. Daily administrations of YMJd (100 mg/kg, i.p.) for 21 consecutive days produced significant reversals of ibotenic acid-induced deficit in learning and memory. The cDNAs from the hippocampi of YMJd and rat control groups were applied to an Incyte rat GEM2 cDNA microarray. The microarray results showed that transthyretin and PEP-19 were abundantly expressed in the YMJd treated group. Importantly, PEP-19 is a neuron-specific protein that inhibits apoptotic processes. On

the other hand, neuronal genes involved in neuronal death or neurodegeneration such as pentraxin and spectrin were abundantly expressed in the control group. Finally, K-WAIS tests, a Korean version of an individual intelligence quotient (IQ) test, and a P300 latency assessment of Event-Related Potential (ERP) were conducted in order to measure changes in cognitive ability before and after 6 weeks of YMJd treatment in normal young adults. The K-WAIS mean scores of the group treated with YMJd were significantly higher than those of the placebo group ($p<0.05$), and their mean P300 latency was substantially shorter ($p<0.005$). These results suggest that YMJd treatment accelerates the speed of information processing and enhances cognitive ability. YMJd treatment may help dementia patients or the elderly recover from cognition deficiencies or degeneration in clinic

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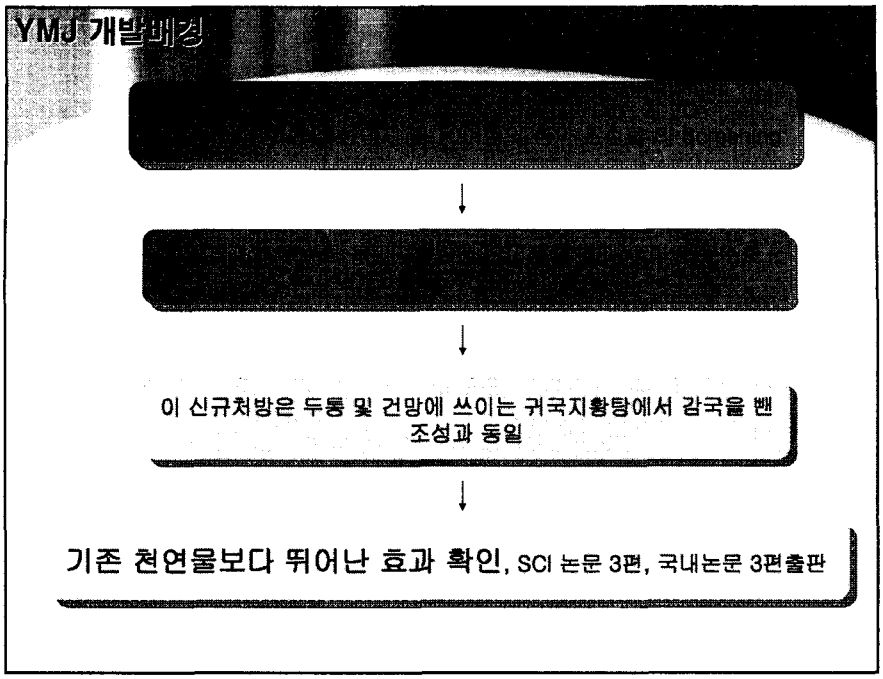
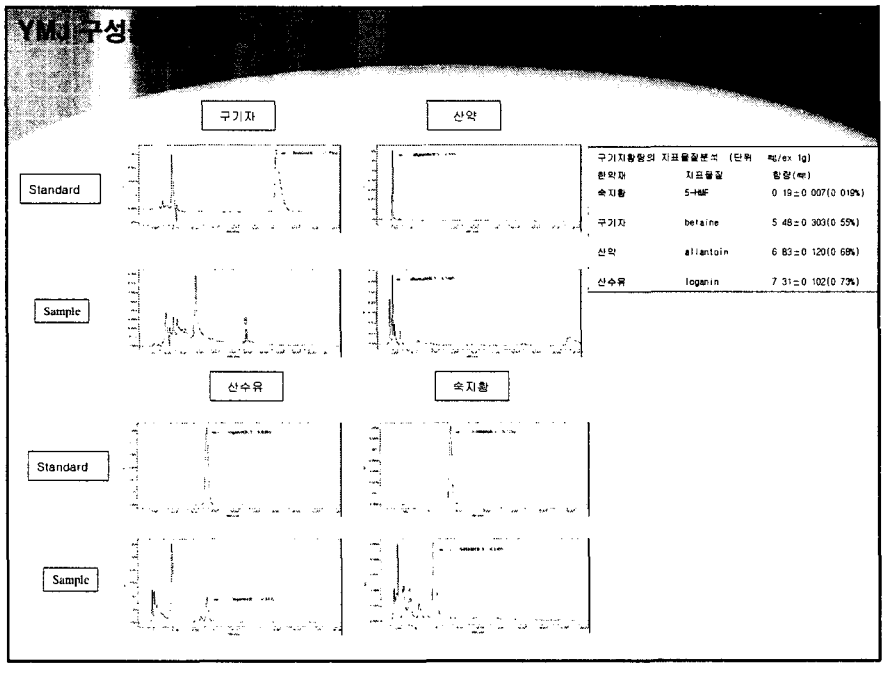
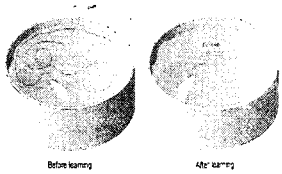
1. Background

- 미국에서는 400만명 이상이 알츠하이머형 치매로 고생하고 있으며 우리나라에서는 노령화 사회로 진입함에 따라 빠른속도로 치매환자들이 증가하고 있음
- 알츠하이머병과 관련된 세계 치매치료제 시장 규모는 2002년 기준 약 4조 6천억원
- 국내치매치료시장 규모는 2000년 약 24억원, 2001년 약 48억원, 2002년도에는 약 125억원의 시장규모로 2년사이 무려 5배나 시장규모가 확대됨
- 그러나, 국내 치매치료제는 외국에서 수입하거나 로열티를 지불하는 것이 대부분임
- 이뿐만 아니라 대부분의 치매치료제의 부작용은 심각한 간독성, 소화 장애 및 운동장애임
- 구기자함량은 전통한방 유래의 새로운 항치매제로 외화 절감 뿐 만 아니라 수천년간 임상 및 예비 임상실험에서 별다른 부작용이 없음이 밝혀져서 안전하면서도 효과 있는 새로운 치매치료제 기대

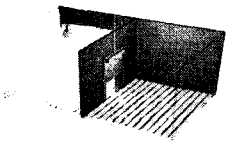

YMJ 개발배경
이 신규처방은 두통 및 건망에 쓰이는 귀국지황탕에서 감국을 뺀 조성과 동일
기존 천연물보다 뛰어난 효과 확인, SCI 논문 3편, 국내논문 3편출판


YMJ 구성
구기자
산약
Standard
Sample
산수유
숙지황
Standard
Sample
구기지황탕의 지표물질분석 (단위 mg/ex 1g)
한약재 지표물질 함량(mg)
숙지황 5-HMF 0.19±0.007(0.019%)
구기자 betaine 5.48±0.303(0.55%)
산약 allantoin 6.83±0.120(0.68%)
산수유 loganin 7.31±0.102(0.73%)

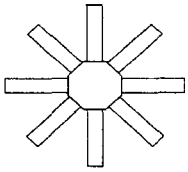
Morris water maze



Passive avoidance



Radial arm maze



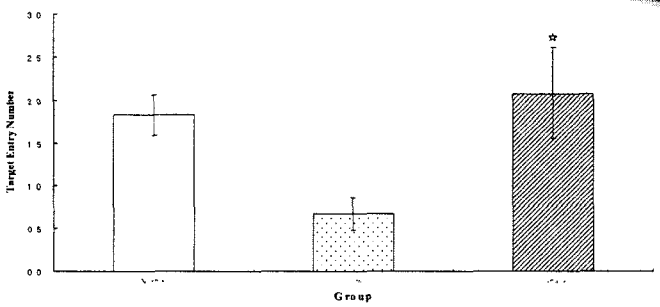


Fig. 6. Target entry number of each group in Morris water maze

Normal: group of rats without any treatment

Control: group of rats treated with L-NAME

Sample: group of rats administrated to YMJ in the presence of L-NAME pretreatment

☆: $p < 0.05$ by student t-test

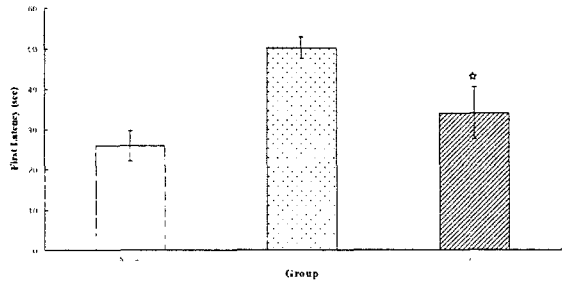


Fig. 7. First latency of each group in Morris water maze

Normal: group of rats without any treatment

Control: group of rats treated with L-NAME

Sample: group of rats administrated to YMJ in the presence of L-NAME pretreatment

☆: $p < 0.05$ by student t-test

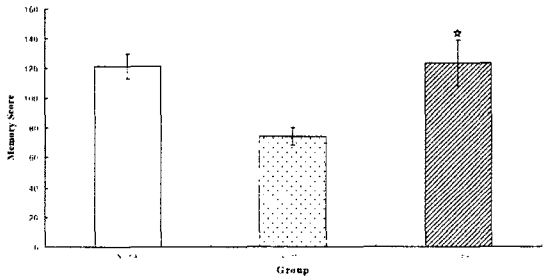


Fig. 8. Memory score of each group in Morris water maze

Normal: group of rats without any treatment

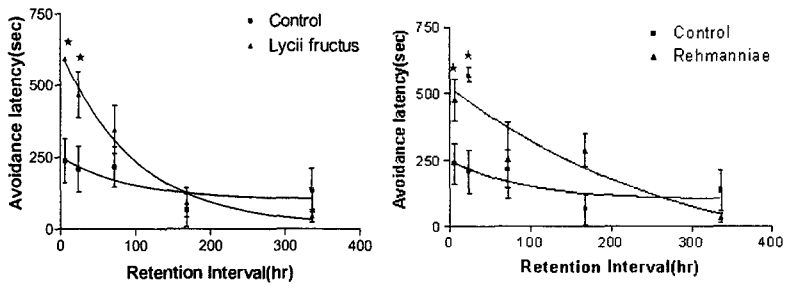
Control: group of rats treated with L-NAME

Sample: group of rats administrated to YMJ in the presence of L-NAME pretreatment

☆: $p < 0.05$ by student t-test

Trial	1	2	3	4	5	6
Normal	7.83±0.11[a]	7.83±0.17	7.67±0.22	7.08±0.65	6.33±0.89	7.67±0.33
Control	0.93±0.59	3.57±0.90	4.07±1.03	4.29±3.85	4.14±1.07	4.43±1.03
Sample	3.11±1.13	5.78±1.01	5.56±1.02	7.11±0.89	7.44±0.41	7.78±0.22
p value	0.07	0.13	0.32	0.06	0.01*	0.01*

a) mean ± SE
Normal: Group of normal rats without any treatment
Control: Group of rats treated with L-NAME
Sample: Group of rats administered *Yukmijihwangtang* in the presence of L-NAME pretreatment
*: $p<0.05$ by student t-test



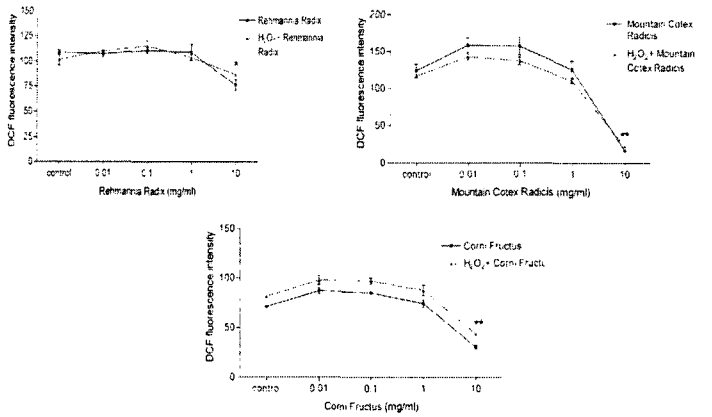


Fig. 2. ROS measurement of PC12 cells in medium containing various concentration of each herbal extract after 24hr. ROS of each samples were quantified by DCF fluorescence intensity (excitation 485 nm / emission 538 nm). Error bars indicate S.E.M. * $P<0.05$ vs. respective control. ** $P<0.01$ vs. respective control.

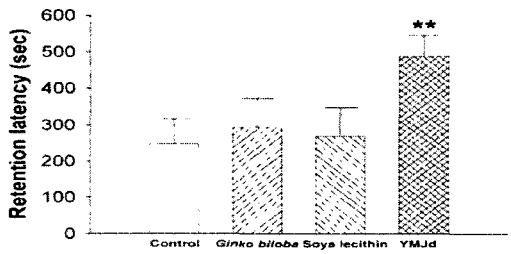


Fig. 1. The Retention Latency of the Passive Avoidance Response

The retention test was performed 24 h after the training session. Control group, rats without any treatments ($n=10$). *Ginko biloba* group, rats administered 2.6 mg per 100 g of body weight a day of *Ginko biloba* for 10 d ($n=10$). Soya lecithin group, rats administered 10 mg per 100 g of body weight a day of Soya lecithin for 10 d ($n=10$). YMJd group, rats administered 400 mg per 100 g body weight a day of YMJd for 10 d ($n=12$). Vertical bars represent Median±Quartiles of retention latencies. ** Significantly different from control group ($p<0.01$) based on Mann Whitney test.

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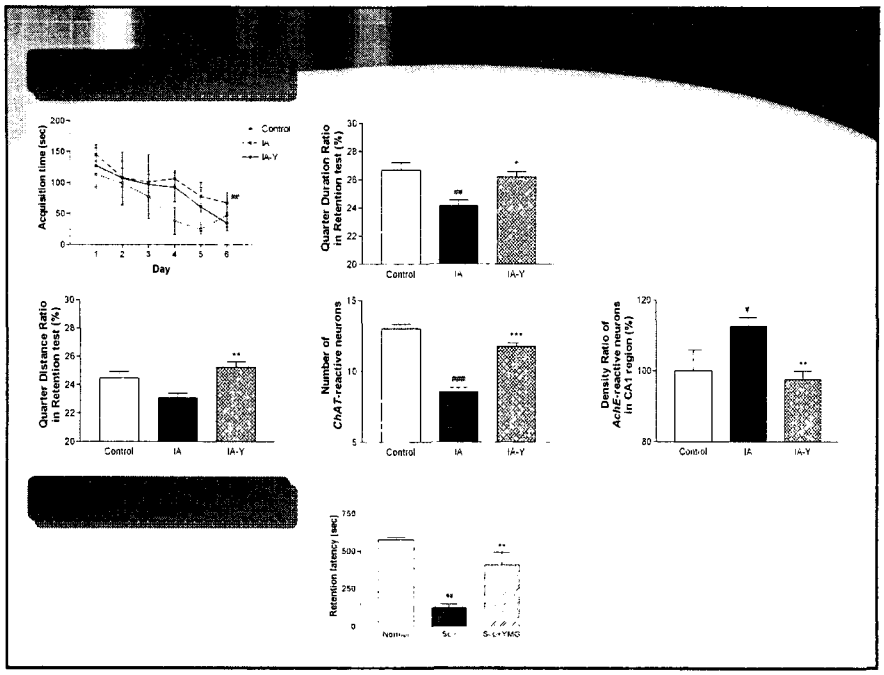
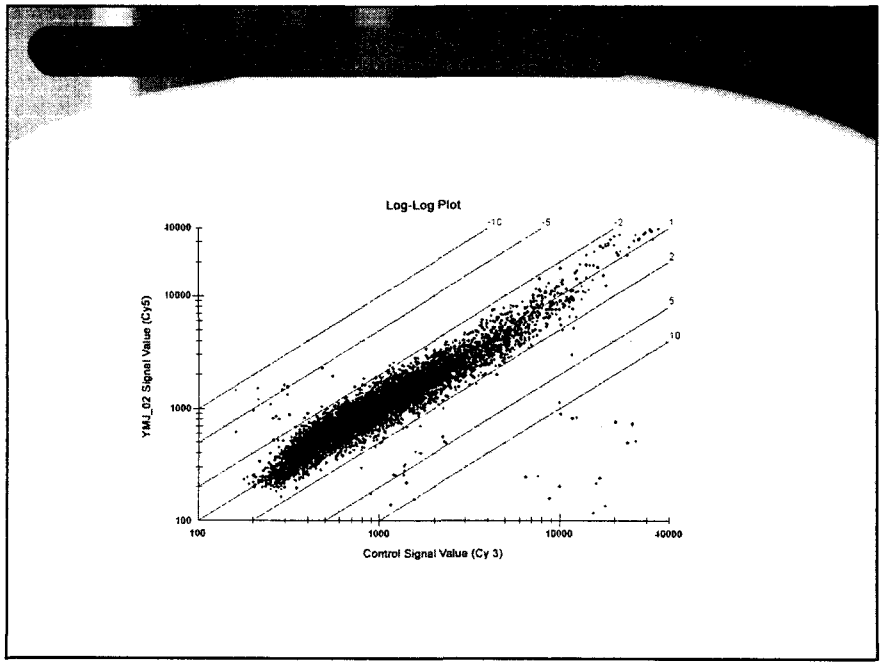
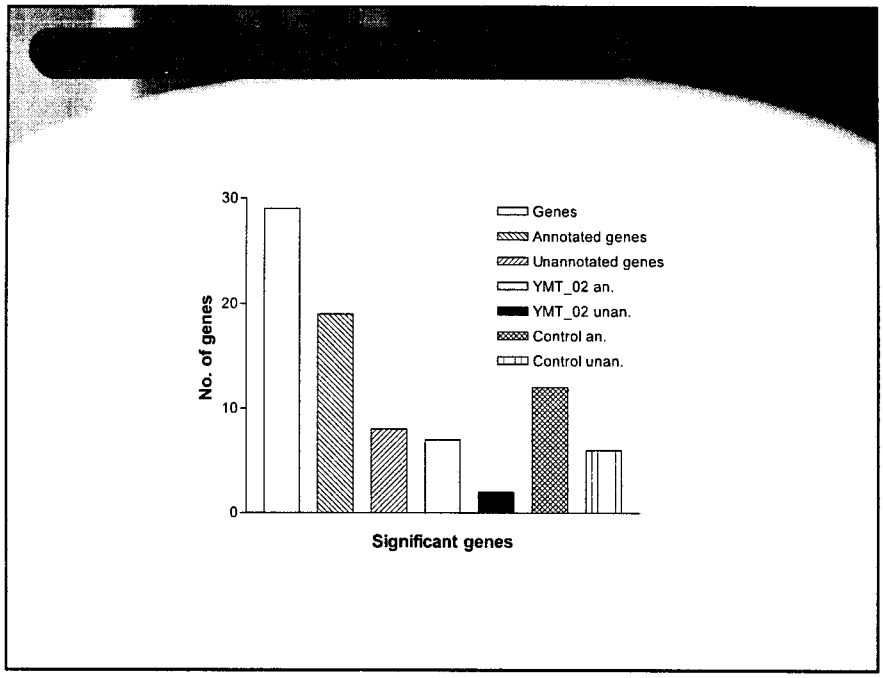
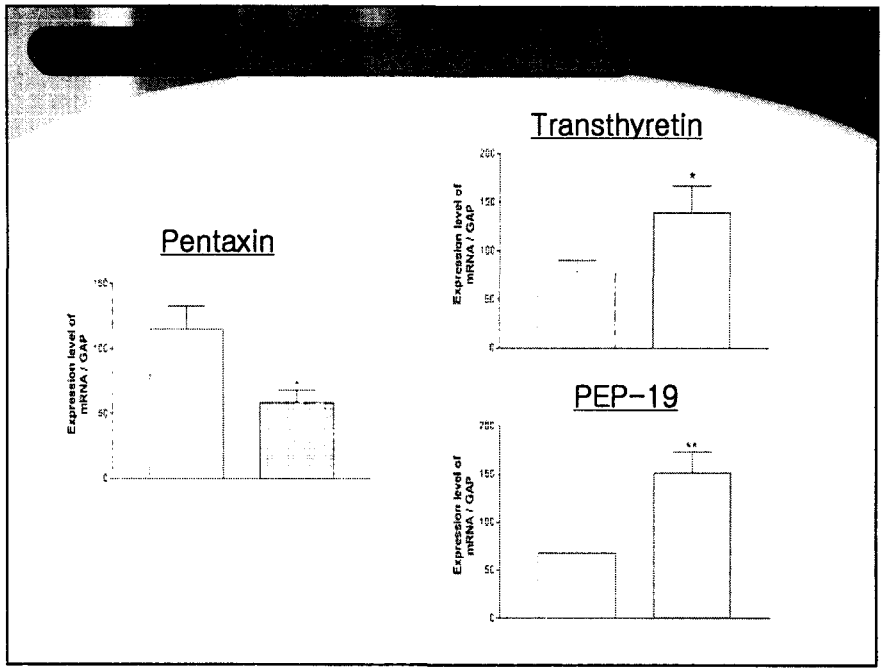
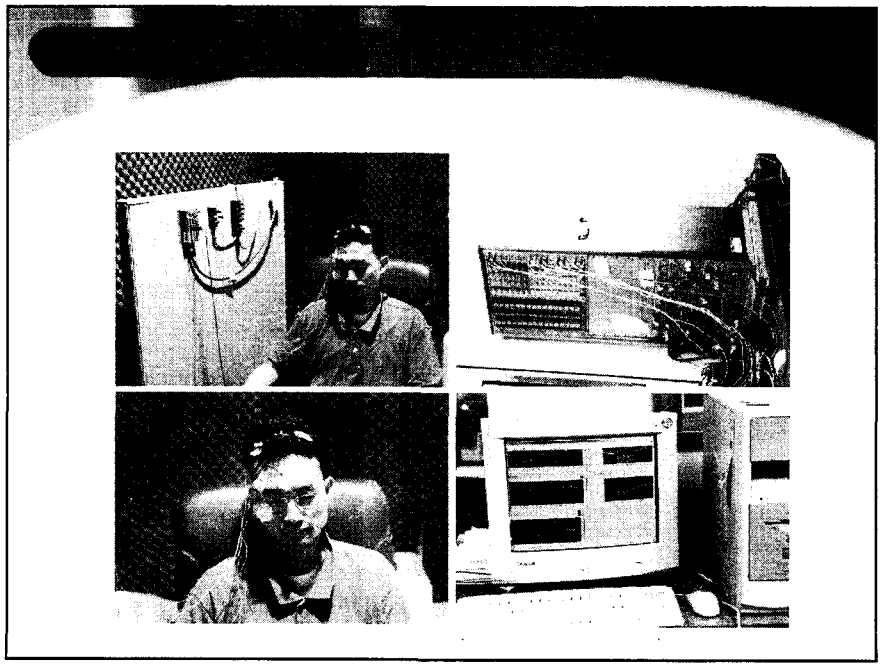

Acquisition time (sec)
Day
Control
IA
IA-Y
Quarter Duration Ratio in Retention test (%)
Quarter Distance Ratio in Retention test (%)
Number of ChAT-reactive neurons
Density Ratio of AchE-reactive neurons in CA1 region (%)
Retention latency (sec)

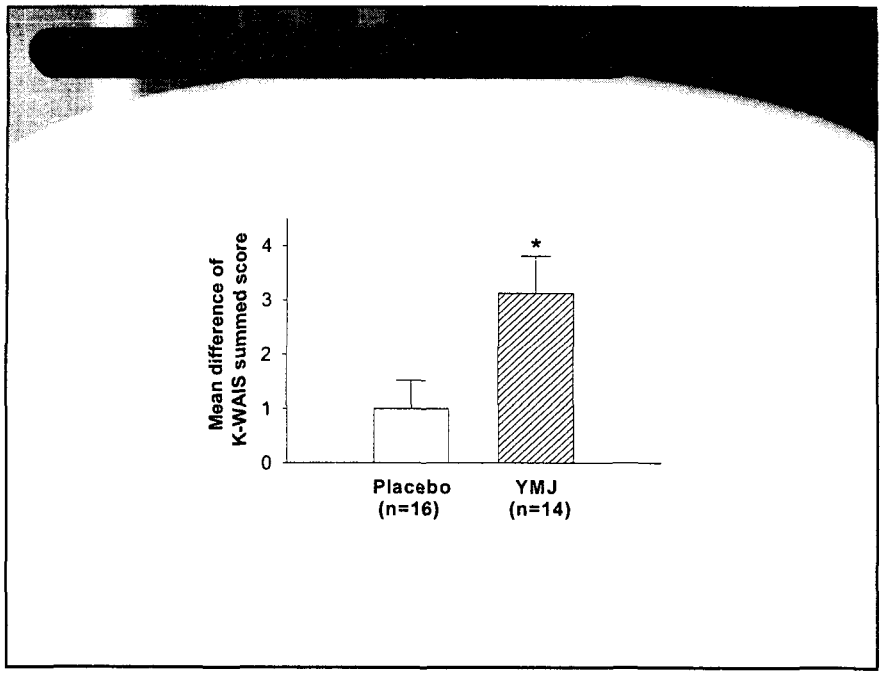

Log-Log Plot
YMJ_02 Signal Value (Cy5)
Control Signal Value (Cy 3)

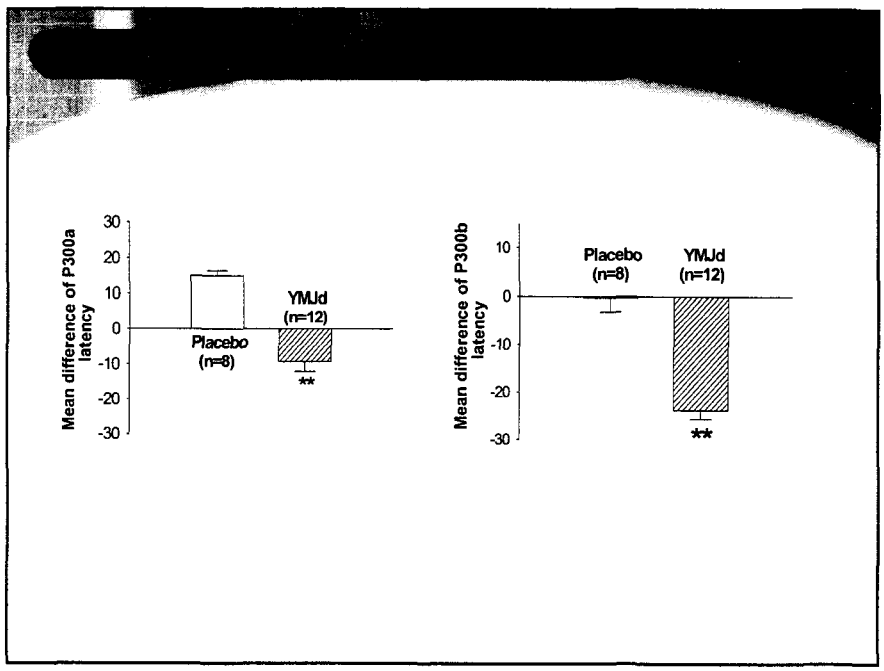


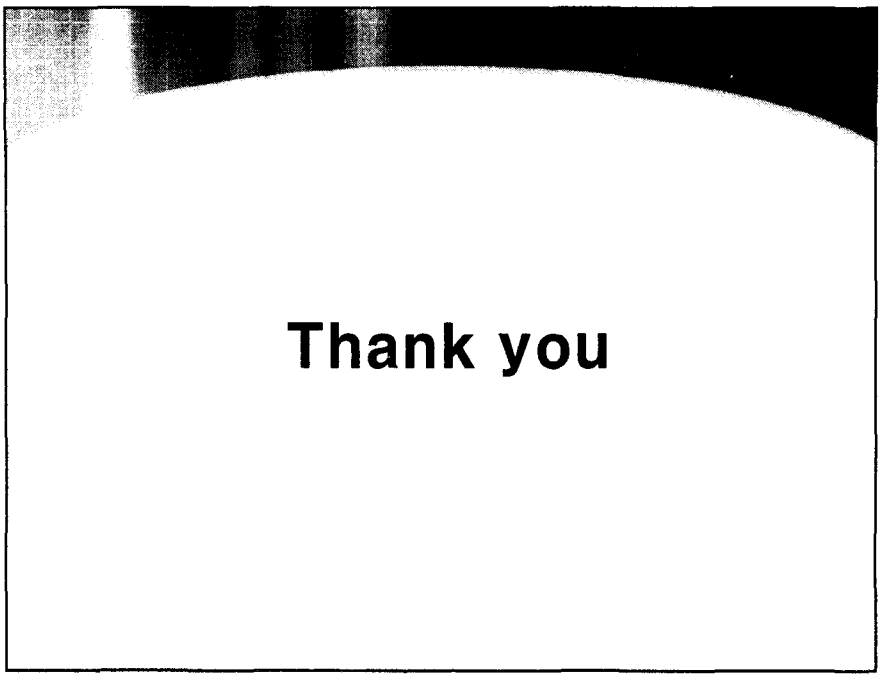
Gene Name	BDE			Genbank*
Rat prealbumin (transthyretin)	-3.2			K03252
Mouse mRNA for type II 57 kd keratin.	-2.2			X03491
Rat phosphotidylethanolamine N-methyltransferase L14441		-2.2		
Rat neuron-specific protein PEP-19	-2.1			M24852
Mouse Purkinje cell protein-4 (Pcp-4)	-2.1			M96359
Rat Axl receptor tyrosine kinase	-2.0			AF046886
Mouse mRNA for type I 47 kd keratin.	-2.0			X03492
Sprague-Dawley (clone LRB9) RAB15 mRNA	2.0			M83679
Rat glutamate receptor subunit 2 (GLUR2) non-NMDA mRNA	2.0			M85035
Mouse p19 mRNA, complete cds. U17259		2.0		
Rat CDK108 mRNA.	2.0			Y17328
Rat neuronal olfactomedin-related ER localized protein (D2Sut1e) U03414		2.1		
Mouse A-X actin	2.1			J04181
Rat alpha-actin cardiac protein.	2.1			X80130
Rat calcium/calmodulin-dependent protein kinase type II alpha-subunit	2.3			J02942
membrane glycoprotein M6	2.3			S65735
Rat spectrin-like protein GTRAP41 AF225960		2.3		
Rat neuronal pentraxin precursor U18772		2.4		


Transthyretin
Expression level of mRNA / GAP
Pentaxin
Expression level of mRNA / GAP
PEP-19
Expression level of mRNA / GAP




Mean difference of K-WAIS summed score
4
3
2
1
0
*
Placebo (n=16)
YMJ (n=14)


Mean difference of P300a latency
30
20
10
0
-10
-20
-30
Placebo (n=8)
YMJd (n=12)
**
Mean difference of P300b latency
10
0
-10
-20
-30
Placebo (n=8)
YMJd (n=12)
**


Thank you