Royal jelly improves mental health

Noriyuki Iegaki, Yukio Narita, **Noriko Hattori, and** Kenji Ichihara

Nagaragawa research center, API Co., Ltd.

email: ichihara-kenji@api3838.co.jp

Royal jelly is a functional food

Final dosage forms




- **Many products mixed with royal jelly have been on sale as a functional food in Japan , and their dosage forms are tablets, granules, capsules, and beverages.**
- **Expected effects**
  - ✓ **Health promotion**
  - ✓ **Recovering from exhaustion**
  - ✓ **Reliving menopausal symptoms**
  - ✓ **Cosmetic effects etc.**

Topics

1. Clinical effect of royal jelly on mental health
2. Supporting studies for the clinical effect of royal jelly
   a. Stress-responding endocrine system
   b. Neurogenesis in the hippocampus

Clinical study of Royal jelly

Study design: randomized, double-blind, placebo-controlled, before-after trial
(*Morita H et al. Nutr J. Sep 21;11:77, 2012*)

Subjects: healthy elderly volunteers

	Placebo	RJ
Subjects (M, F)	30 (17, 13)	31 (17, 14)
Age	70.1 ± 10.8	70.4 ± 8.5

Test substance: fresh RJ

Dosage and administration: 3000 mg/day, oral ingestion

Administration period: 6 months

Evaluation method: physiological tests, laboratory (blood) tests, and questionnaire

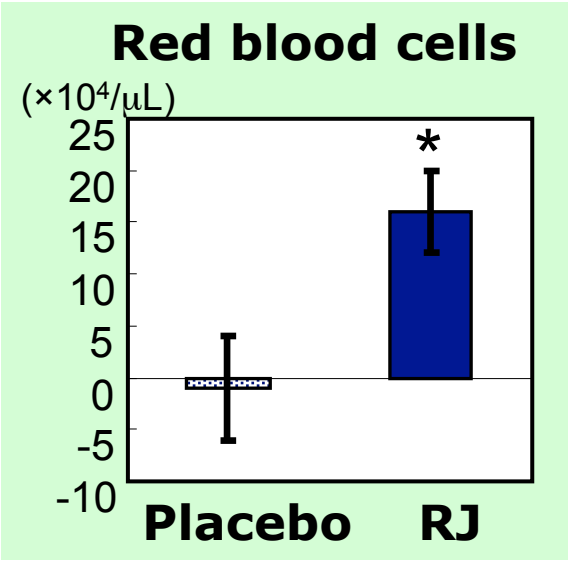
Examination items in physiological and laboratory tests

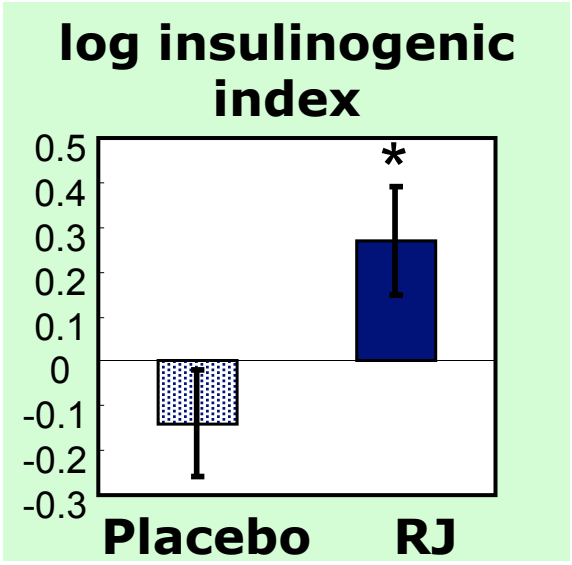
Metabolic syndrome		Hemocyte	QOL（SF-36）	Others
TC	Glu0	WBC	PF	BMI
LDL	Glu30	RBC	RP	Waist circumference
HDL	Glu120	Ht	BP	SBP
TG	HbA1c	Hb	GH	DBP
nonHDL-cho	Insulinogenic index	PLT	VT	8OHDG/CRE
Adiponectin(HMW)	IRI0		SF	MHPG
Homocysteine	IRI30		RE	TP
hsCRP	HOMA-R		MH	ALB
Pulse wave velocity	Leptin			cCa
				eGFR

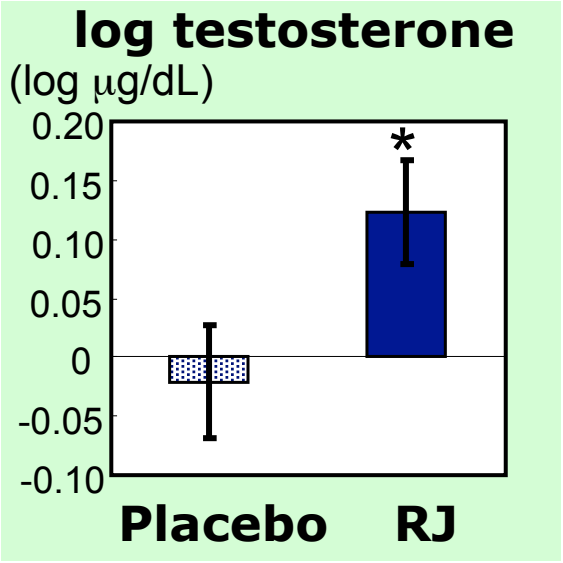
Hormone	Bone	Kidney	Liver, Bile duct	Kraepelin test
Estradiol	NTX	UA	AST	
Testosterone	ucOC	CRE	ALT	
DHEAS	Ca	BUN	gGT	
Prolactin	IP	Cystatin C	ALP	
	BMD			

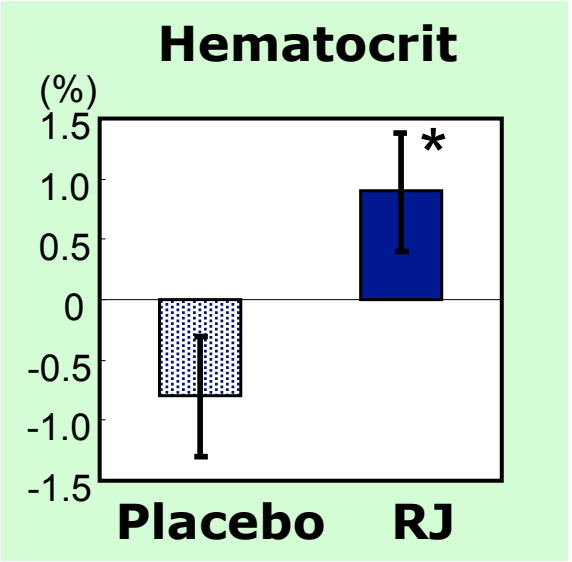
Differences before and after **the intervention** were **compared** between **two groups.**

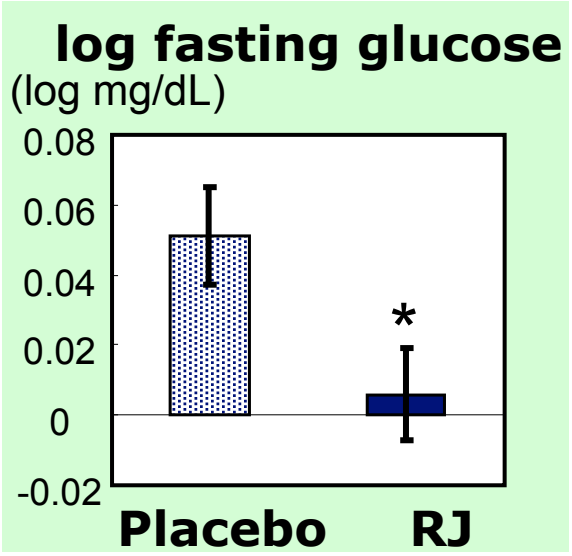
Significant effects of Royal jelly on physiological and laboratory items

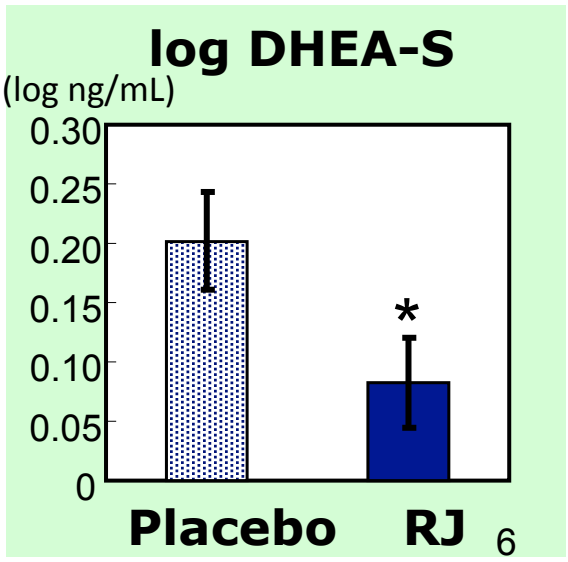












Health quality measures with the SF-36 health survey questionnaires

The SF-36 health survey evaluates the following 8 points:
physical functioning, physical role functioning, bodily pain, general health perceptions, vitality, social role functioning, emotional role functioning, and mental health.

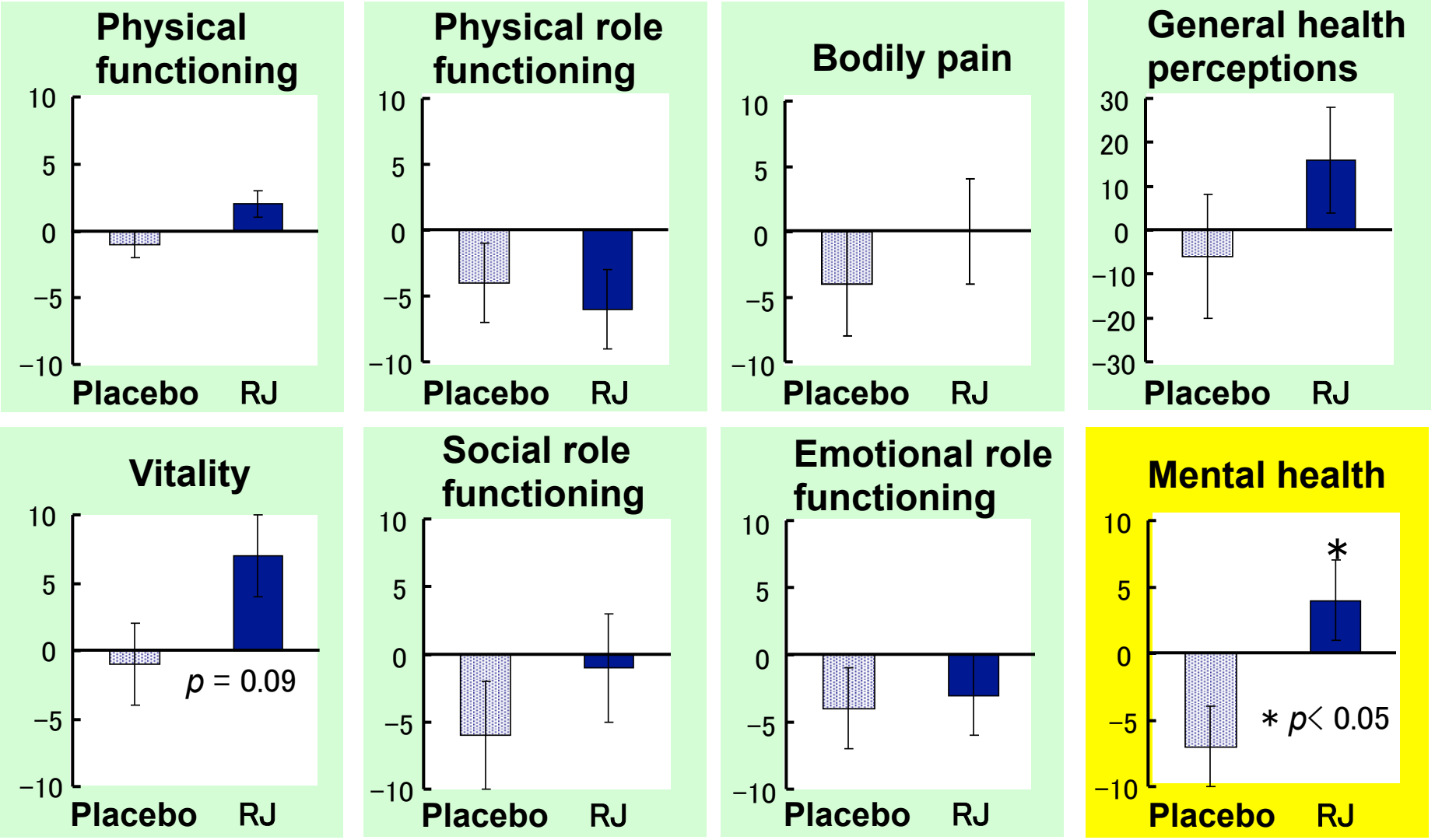
Example

(Circle One Number on Each Line)						
Did you feel full of pep?	1	2	3	4	5	6
Have you been a very nervous person?	1	2	3	4	5	6
Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
Have you felt calm and peaceful?	1	2	3	4	5	6
Did you have a lot of energy?	1	2	3	4	5	6
Have you felt downhearted and blue?	1	2	3	4	5	6
Did you feel worn out?	1	2	3	4	5	6
Have you been a happy person?	1	2	3	4	5	6
Did you feel tired?	1	2	3	4	5	6

Evaluation criteria
1: All of the time
2: Most of the time
3: A good bit of the time
4: Some of the time
5: A little of the time
6: None of the time

(http://www.rand.org/health/surveys_tools/mos/mos_core_36item_survey.html)

Effects of **royal jelly** on subjective e**valuation** score**s for health survey**



Summary of the first topic

- **In the clinical study, royal jelly improved**
  - **erythropoiesis,**
  - **glucose tolerance, and**
  - **mental health.**

- **In order to support the clinical effect on mental health, we have been investigating its mechanisms in laboratory studies.**

Topics

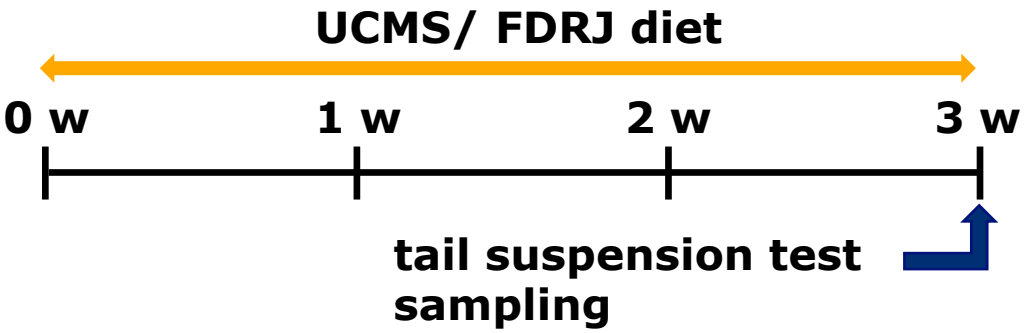
1. Clinical effect of royal jelly on mental health

2. **Supporting studies for the clinical effect of royal jelly**

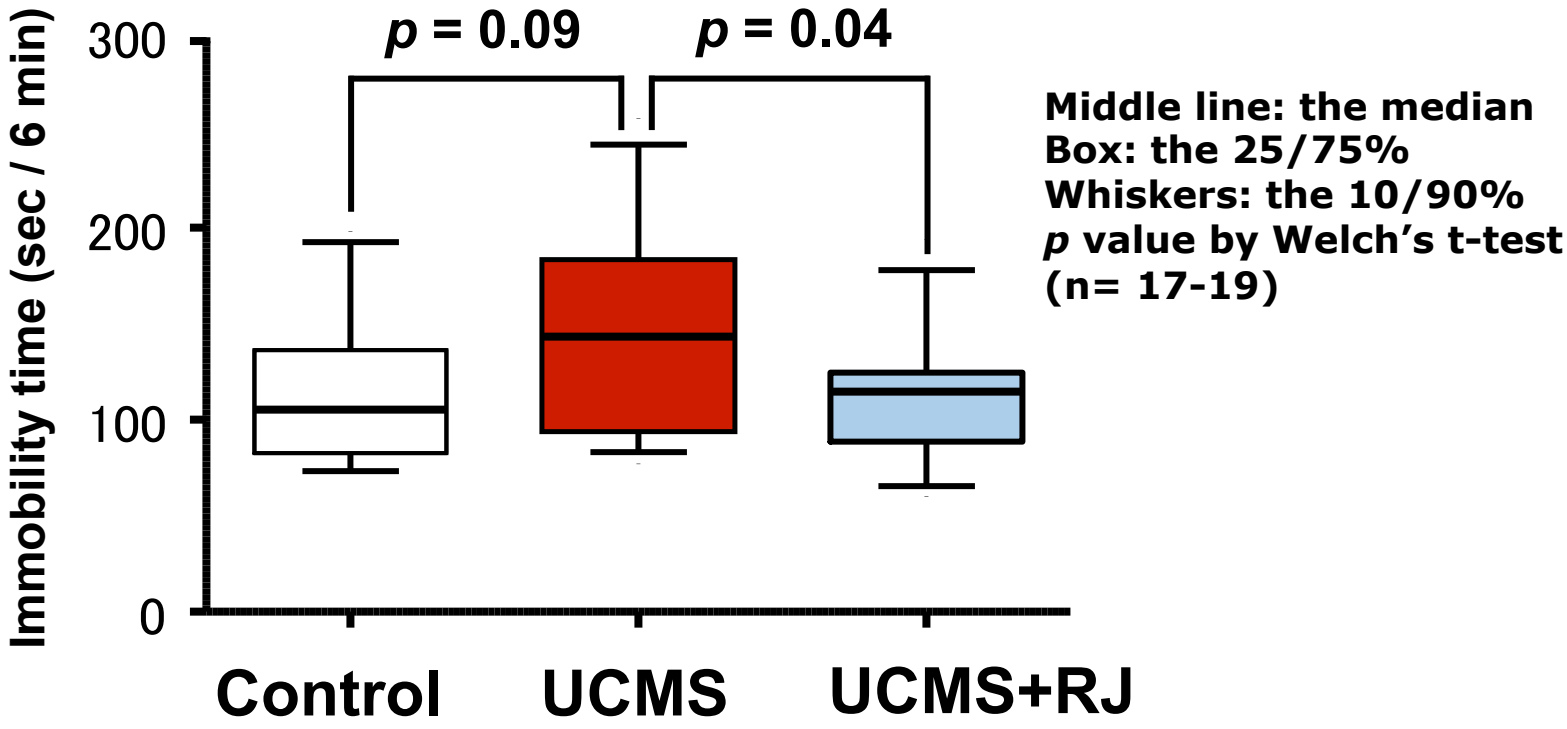
   a. **Stress-responding endocrine system**

   b. Neurogenesis in the hippocampus

Study of the unpredictable chronic mild stress (UCMS) model of depression

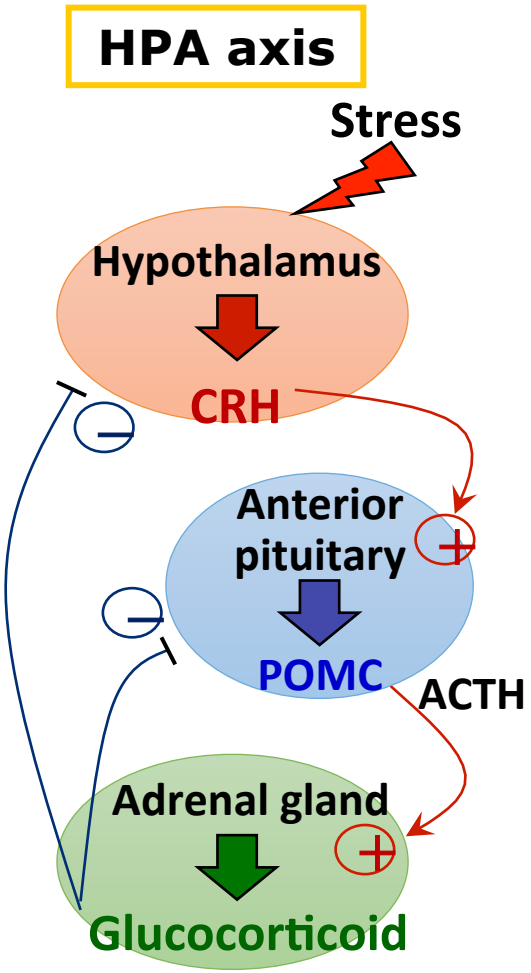
• Animal	BALB/c male mice
• Test compound	4% freeze-dried RJ powder (FDRJ)
• Administration route	oral (mixed in a basal diet)
• UCMS items	wet bedding, no bedding, tilted cage, the light/dark cycle inversion, illumination during dark phase, food deprivation, water deprivation, restraint, forced swimming
• Test schedule Experimental groups • control (non-UCMS) • UCMS • UCMS+RJ	
• Examination	immobility time in tail suspension test, gene expression, microarray analysis

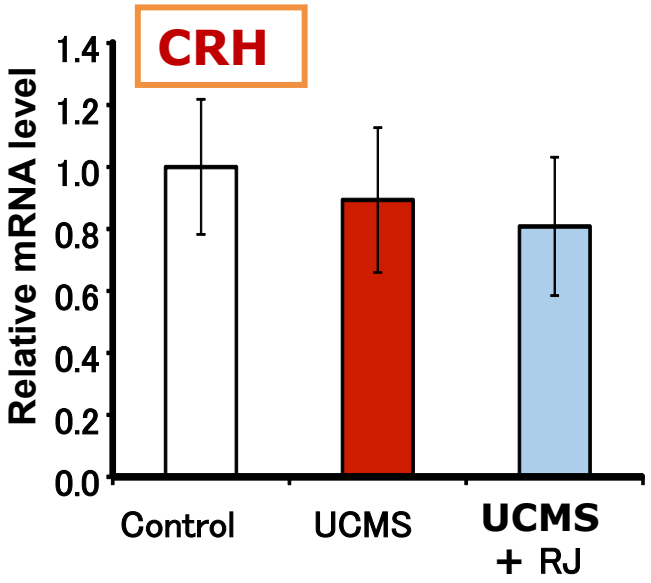
Effect of RJ on immobility time in UCMS-exposed mice

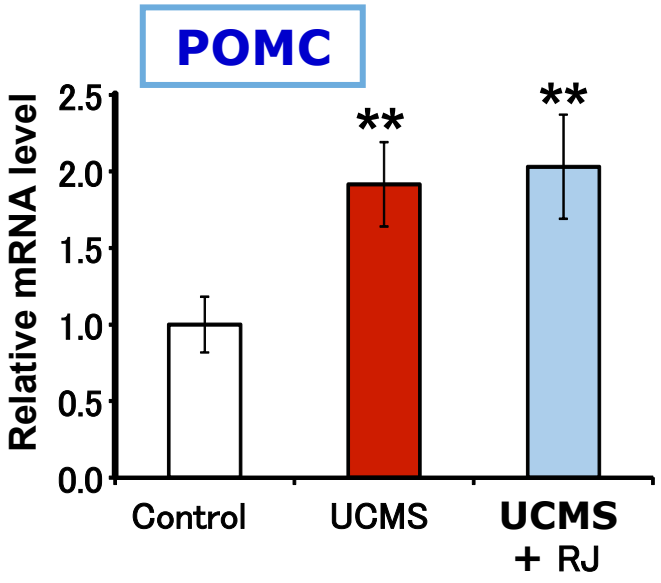


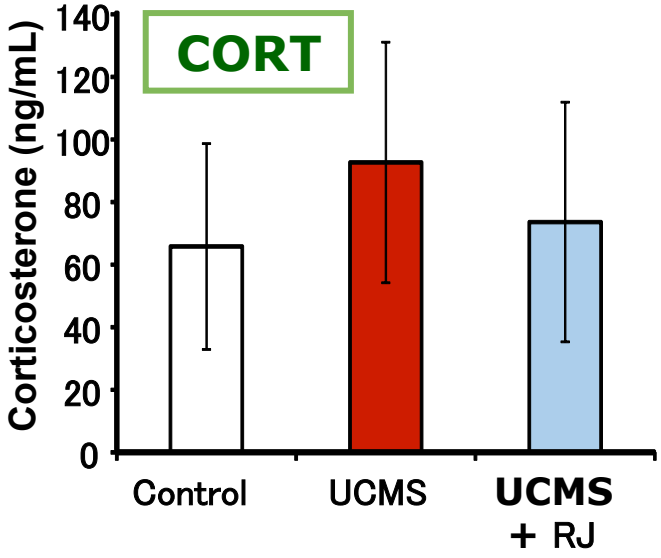
The RJ-fed, stressed group didn't show depressive behavior caused by stress exposure.

Analysis of gene expressions of stress-responding hormones









n = 9-10, Mean ± SD
** P<0.01 vs. control by Steel test

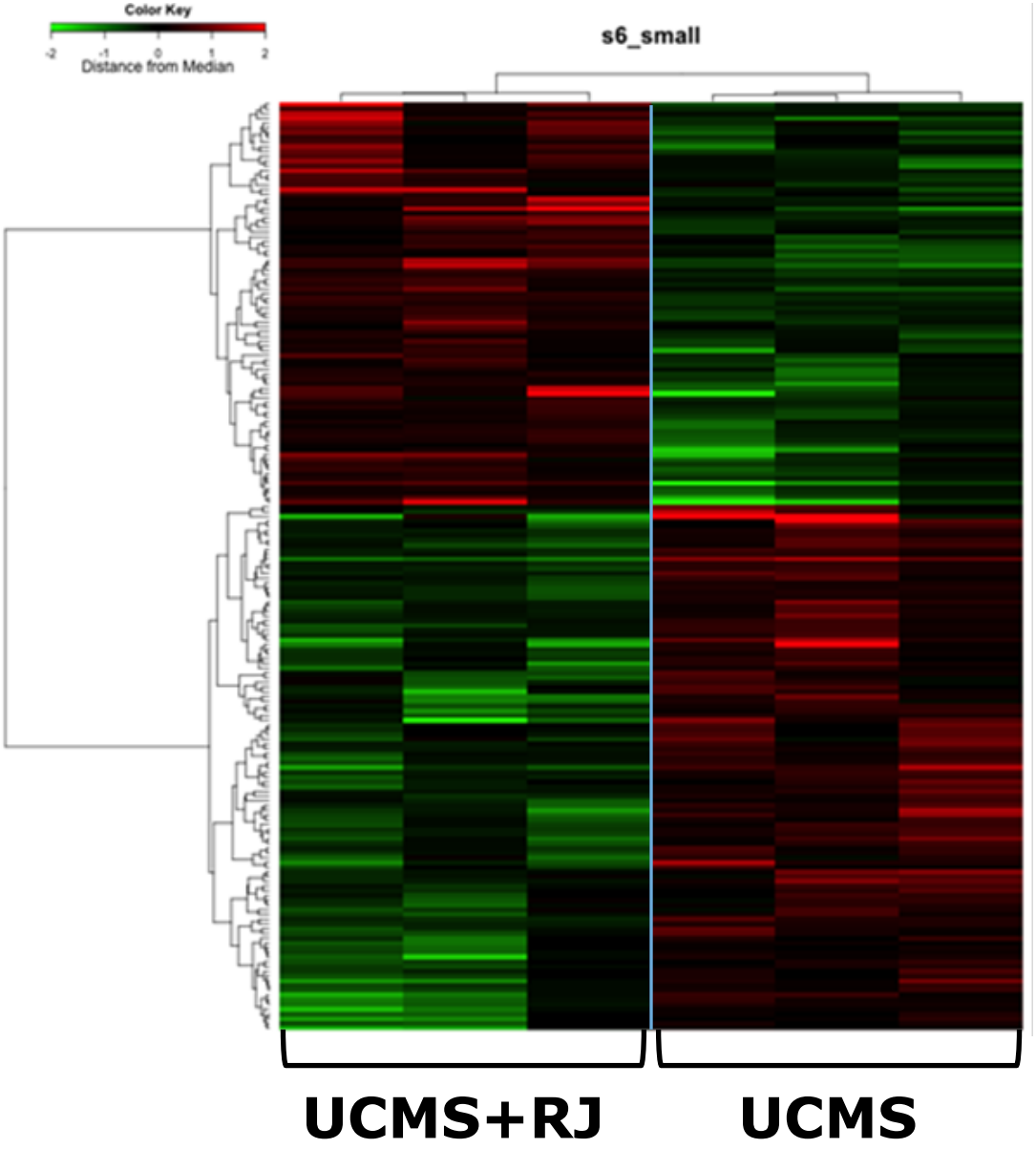
C R H : corticotropin-releasing hormone
POMC: pro-opiomelanocortin
CORT : corticosterone

Microarray analysis of the adrenal gland

- Three representative animals in each group were used for microarray analysis of the adrenal glands.
- The number of changed genes
  - In the stressed group, 1158 genes changed compared with the control group.
  - In the RJ-fed, stressed group, 196 genes changed compared with the stressed group.

comparison	p value	ratio	genes change
Control vs UCMS			29060
	＜0.05		3364
	＜0.05	≧1.5	1158
UCMS vs FDRJ			29060
	＜0.05		951
	＜0.05	≧1.5	196

Cluster analysis of changed genes



Gene ontology (GO) analysis of changed genes

- **Changed genes in the stressed group**
  - **Several changed genes were contained in group of steroid biosynthesis.**

GO that contains much changed genes	Number of gene	%*	P-Value
Steroid biosynthesis	7	0.8	0.000
Terpenoid backbone biosynthesis	6	0.7	0.000
Ubiquitin mediated proteolysis	15	1.6	0.001
Inositol phosphate metabolism	8	0.9	0.005
Focal adhesion	16	1.7	0.012
B cell receptor signaling pathway	9	1	0.014
ECM-receptor interaction	9	1	0.017
Regulation of actin cytoskeleton	16	1.7	0.025
Axon guidance	11	1.2	0.035

*Rate of gene including each GO

Pathway analysis of changed genes

Changed genes in the RJ-fed, stressed group

- **Several changed genes were contained in the PXR/RXR activation pathway involved in detoxification of cholesterol.**

Ingenuity Canonical Pathways	Gene	p-value*
PXR/RXR Activation	NR0B2,ALAS1,PPARGC1A	0.001
Heme Biosynthesis II	ALAS1,	0.014
Tetrapyrrole Biosynthesis II	ALAS1,	0.014
LPS/IL-1 Mediated Inhibition of RXR Function	NR0B2,ALAS1,PPARGC1A	0.022
Estrogen Receptor Signaling	NR0B2,PPARGC1A	0.026
Cell Cycle: G1/S Checkpoint Regulation	MYC,	0.041
Endometrial Cancer Signaling	MYC,	0.041
ErbB2-ErbB3 Signaling	MYC,	0.041
Estrogen-mediated S-phase Entry	MYC,	0.041
FXR/RXR Activation	NR0B2,PPARGC1A	0.041
PPAR Signaling	NR0B2,PPARGC1A	0.044

*Fisher's exact test

Summary of the second topic

- **Study of the chronic stress rodent model of depression**
  - **RJ-fed group did not show an increase in the stress-induced immobility (depressive behavior).**
  - **In the anterior pituitary, a clear increase in *Pomc* mRNA expression was observed in both stressed groups.**
  - **Microarray analysis of the adrenal gland indicated that gene expressions involved in steroid metabolism/ detoxification were changed in the RJ-fed, stressed group.**
  - **These results suggest a possibility that RJ improves the stress-induced depressive symptoms in part through the stress-responding endocrine system.**

Topics

1. Clinical effect of royal jelly on mental health

2. **Supporting studies for the clinical effect of royal jelly**

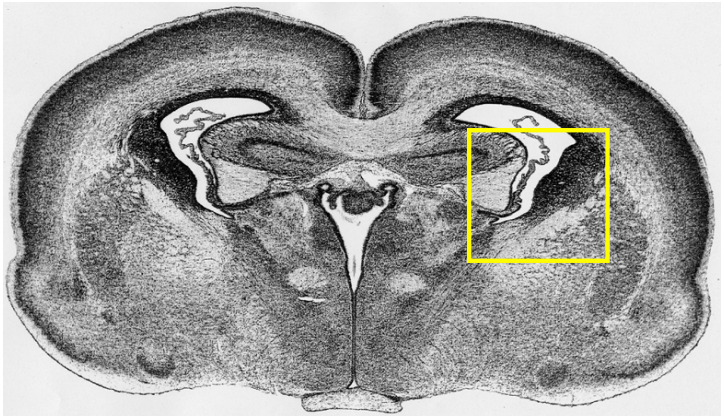
   a. Stress-responding endocrine system

   b. **Neurogenesis in the hippocampus**

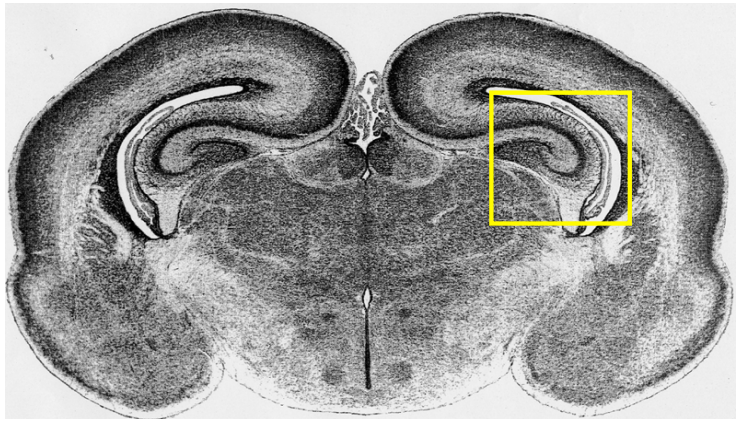
A hypothesis regarding the relationship of hippocampal neurons to depression

Is preservation or promotion of hippocampal neurogenesis effective for prevention and therapy of depression?

- **Hippocampal neurogenesis is suppressed by stress exposure, which probably leads to depression, and restored by chronic antidepressant treatment.**
- **Neural stem/progenitor cells are present in two areas of the adult brain, and they differentiate into neurons.**



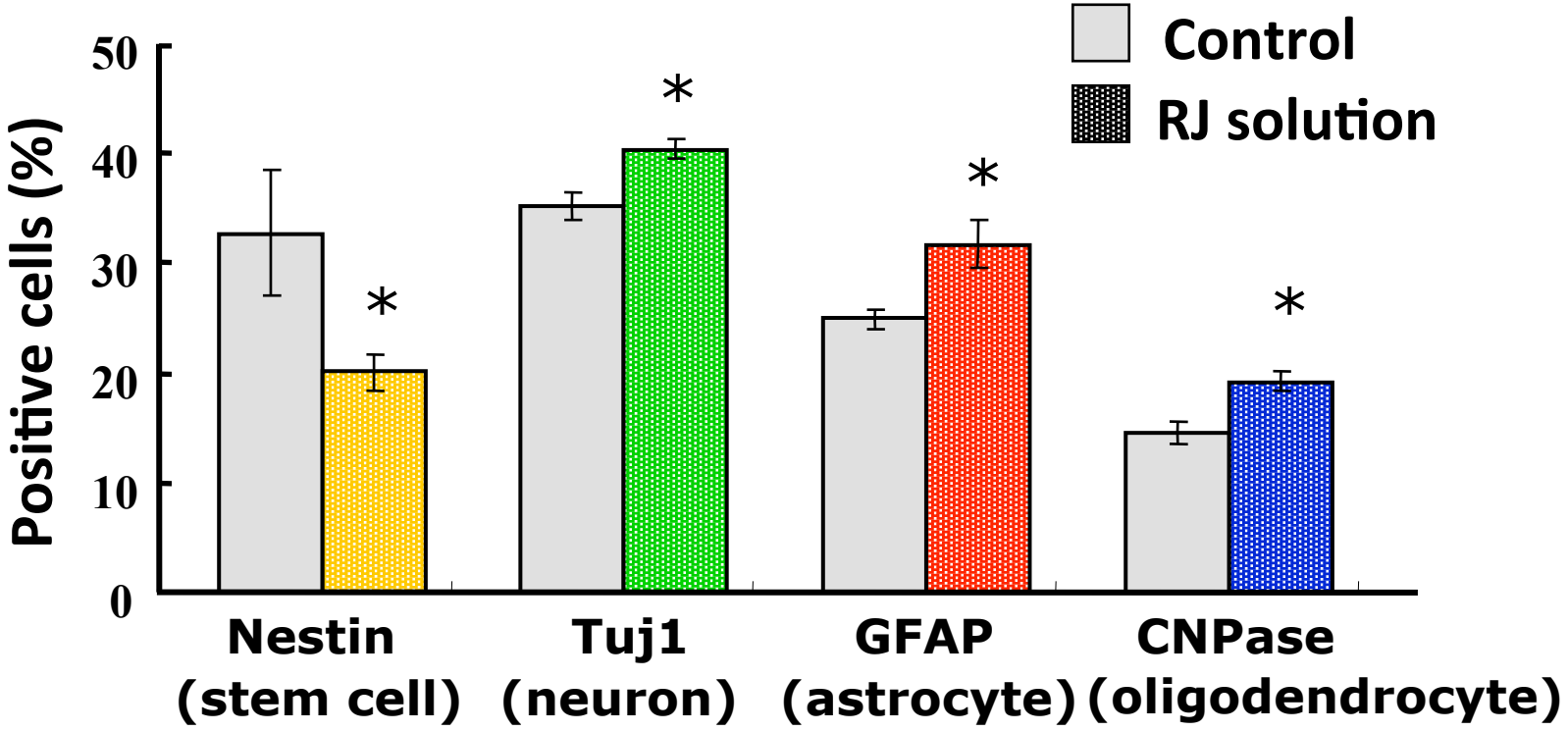
around the lateral ventricles



granular cell layer of the hippocampal dentate gyrus

Effects of RJ on the differentiation of neural stem cells

- **RJ solution increased the rate of cells expressing neuron, astrocyte, and oligodendrocyte markers, and decreased that of undifferentiated cells.**

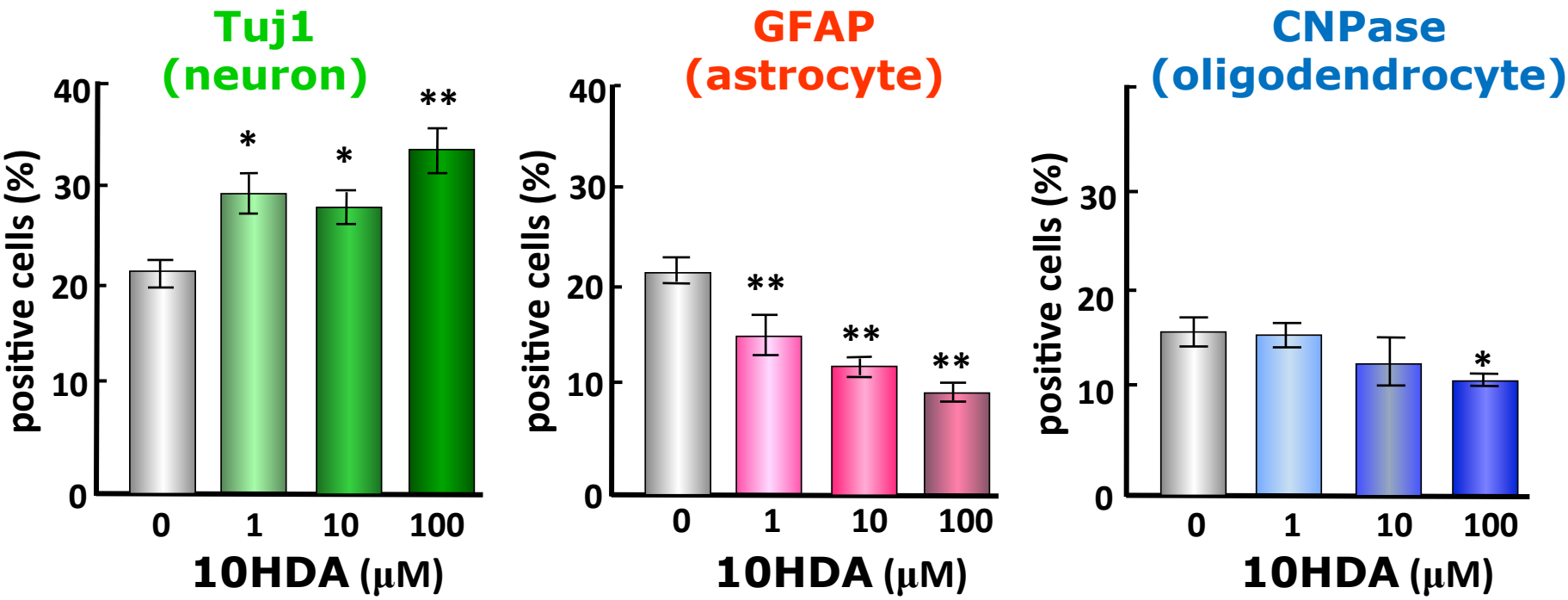


* P < 0.05, RJ vs Control by t-test

Effects of 10HDA on the differentiation of neural stem cells

- **10-hydroxy-trans-2-decenoic acid (10HDA) increased the rate of cells expressing the neuronal marker Tuj1.**

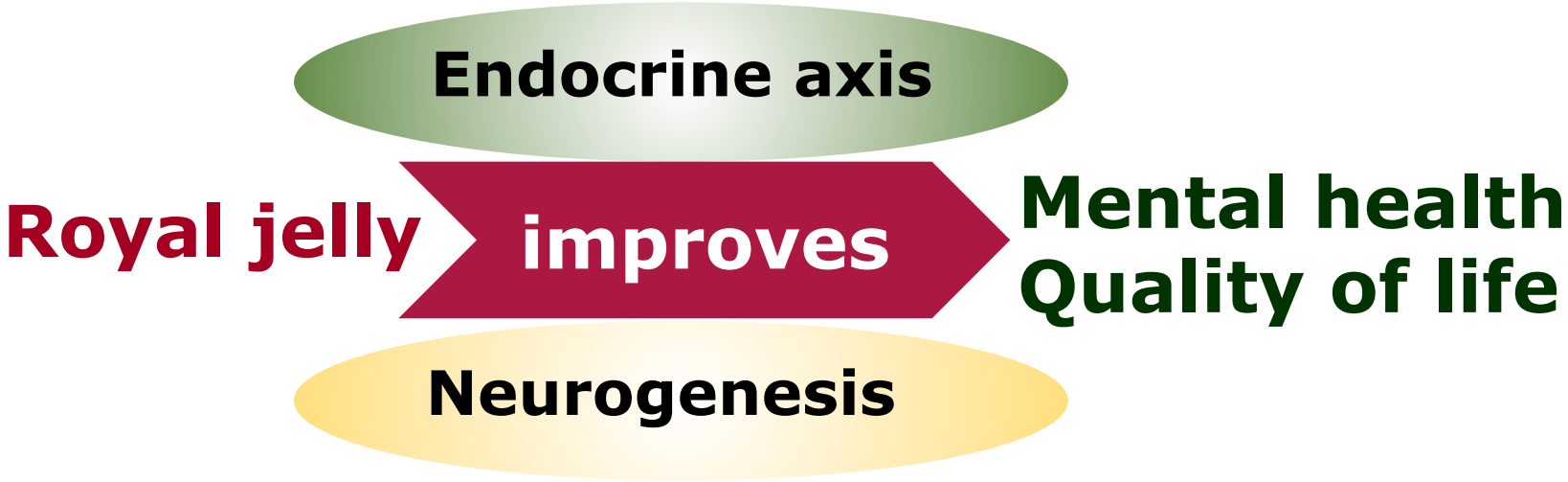
10HDA is thought to be one of the components of RJ for promoting neurogenesis.



*p < 0.05, **p < 0.01 vs Control

Conclusion

- **Royal jelly possibly reduces depressive symptoms**
  - **by acting on the endocrine system, and**
  - **by preserving or promoting neurogenesis in the hippocampus .**



Thank you for your attention