

Royal jelly improves mental health

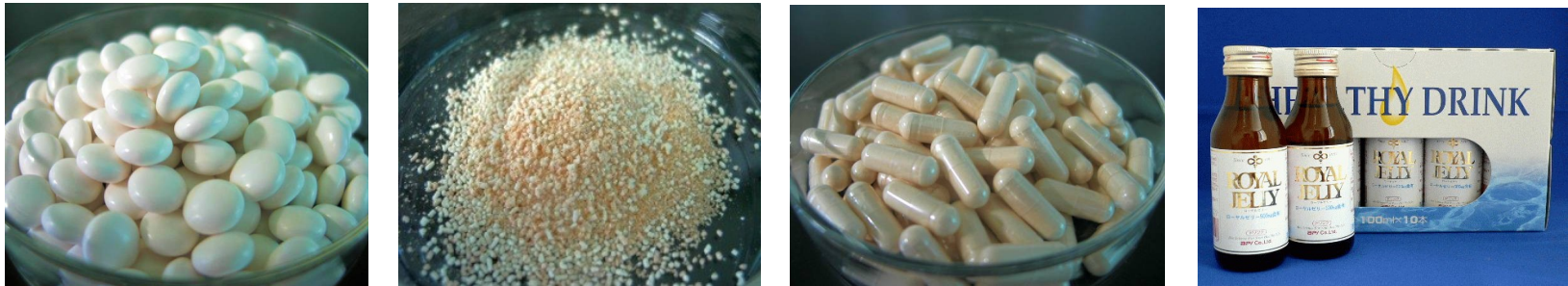
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Royal jelly is a functional food

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

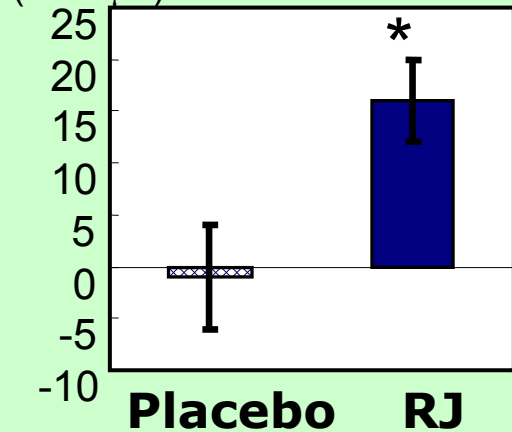
Examination items in physiological and laboratory tests

Metabolic sy			
TC	Glu0		
LDL	C	RBC	
HDL	C	Ht	
TG	H		
	Insulinogenic index		
			MH
Testosterone			
DHEAS			

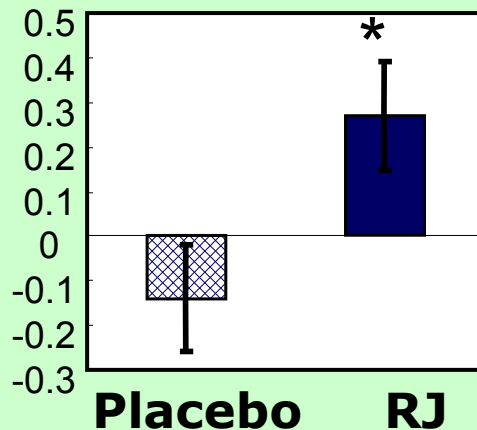
Differences before and after the intervention were compared between two groups.

Significant effects of Royal jelly on physiological and laboratory items

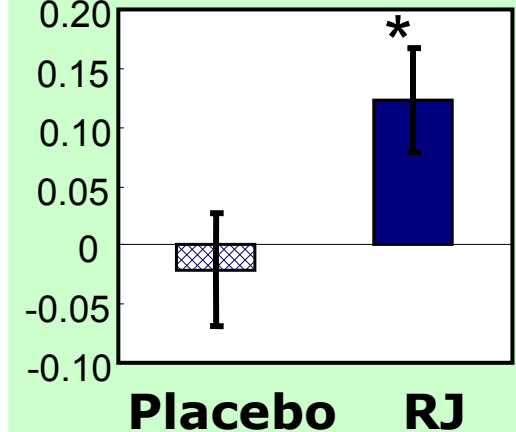
Red blood cells
($\times 10^4/\mu\text{L}$)



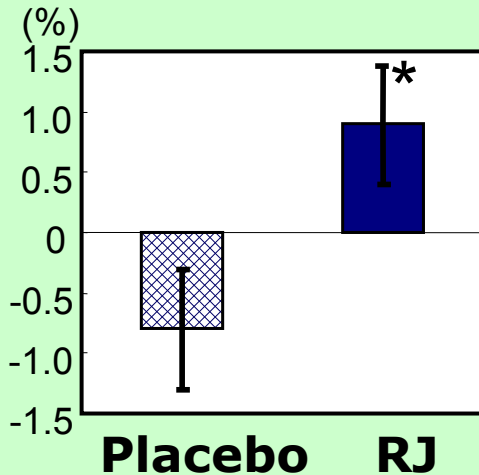
log insulinogenic index



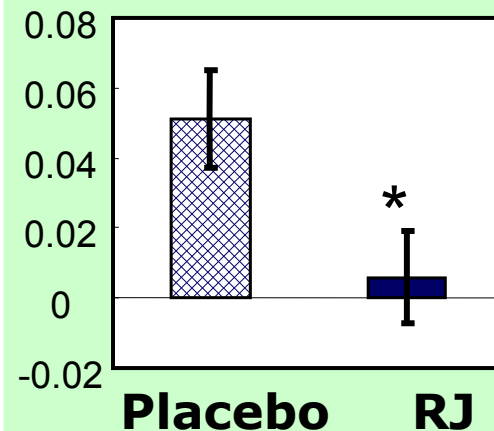
log testosterone
(log $\mu\text{g/dL}$)



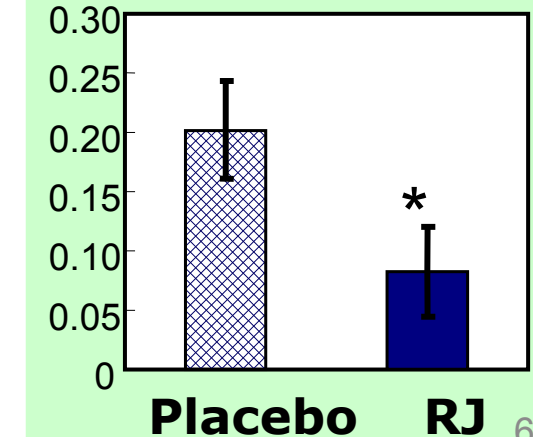
Hematocrit



log fasting glucose
(log mg/dL)



log DHEA-S
(log ng/mL)



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

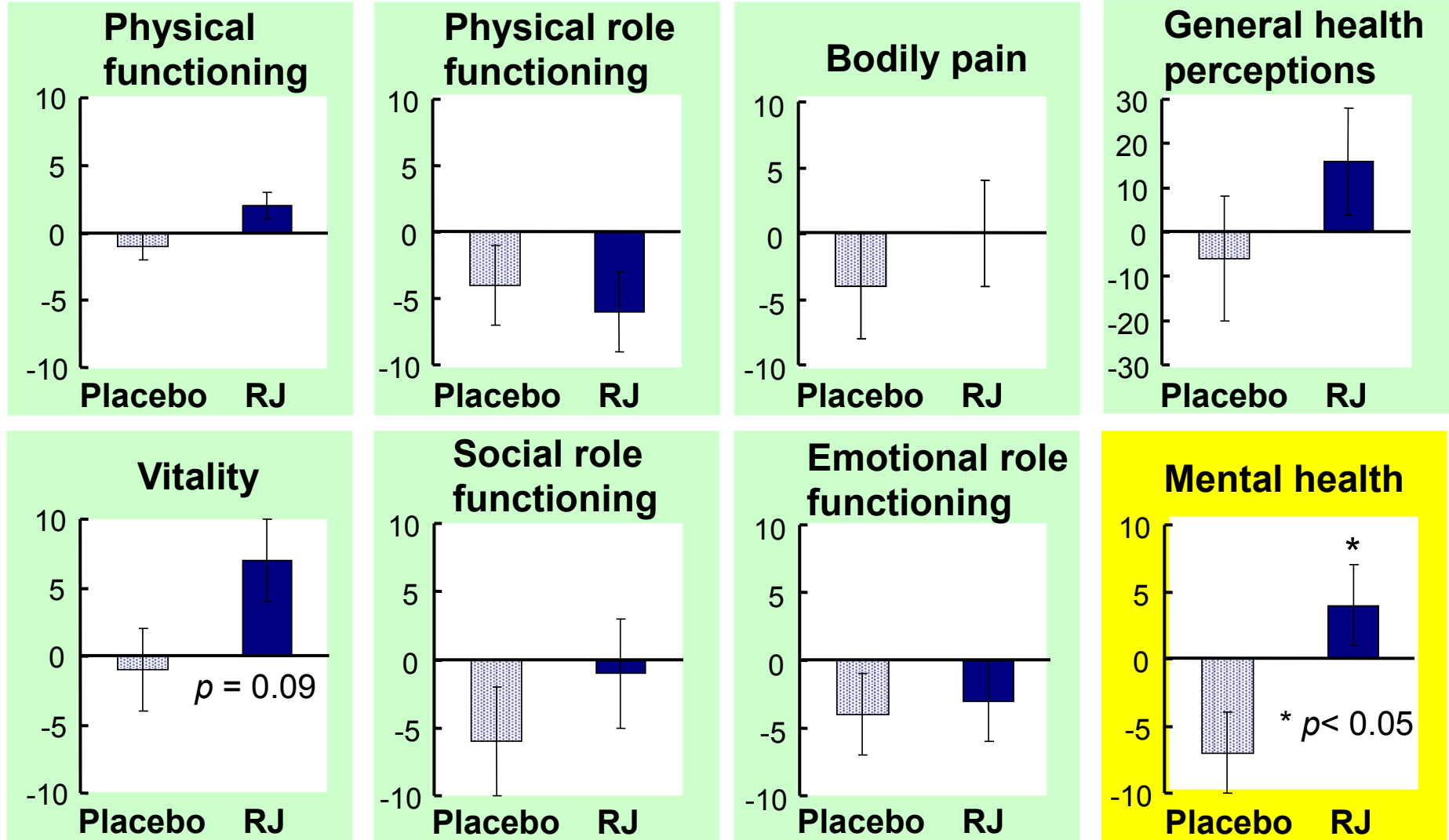
(Circle One Number)
Did you feel full of pep?
Have you been a very nervous person?
Have you felt so down in the last 4 weeks that you could cheer you up?

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 evaluation scores 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.

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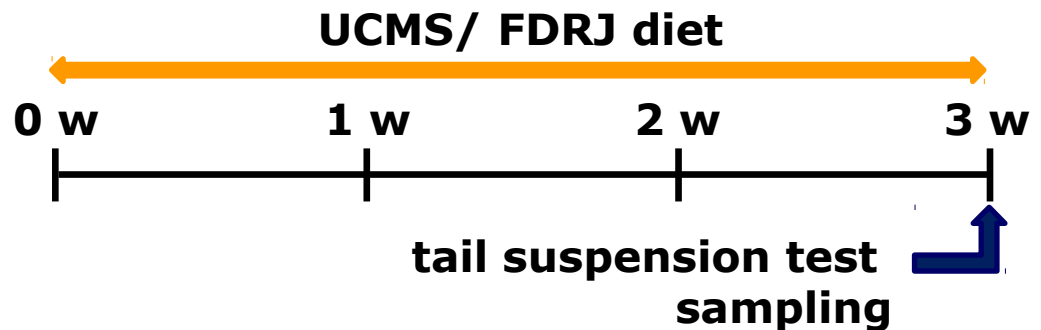
Study of the unpredictable chronic mild stress (UCMS) model of depression

• 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

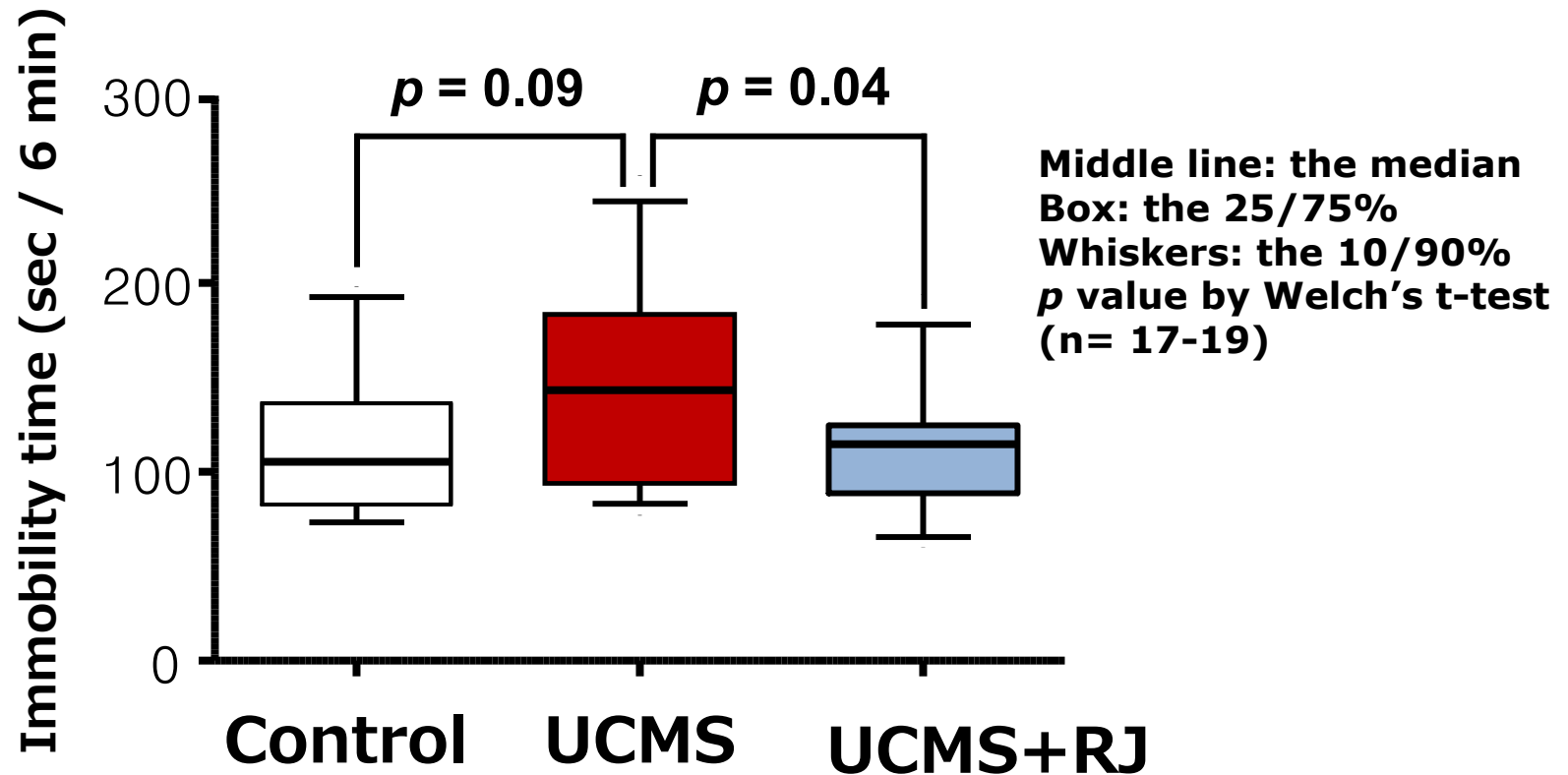
- control (non-UCMS)
- UCMS
- UCMS + RJ



• Examination

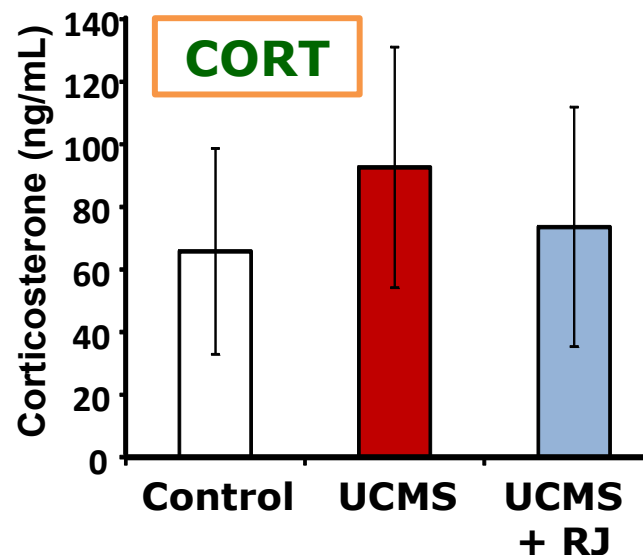
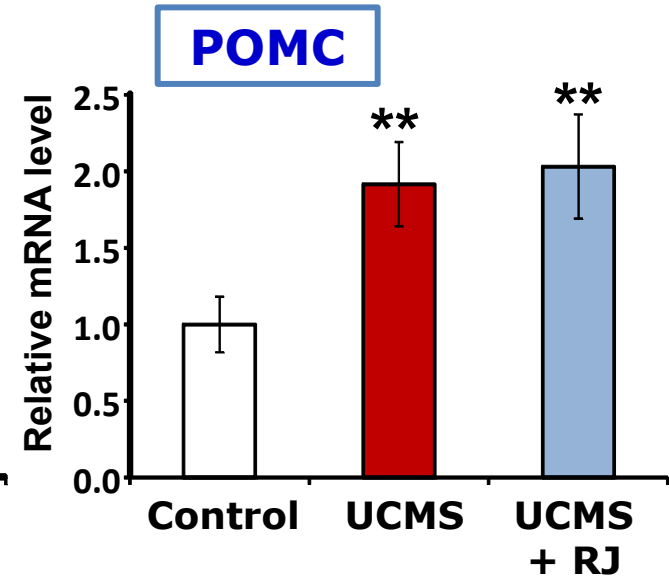
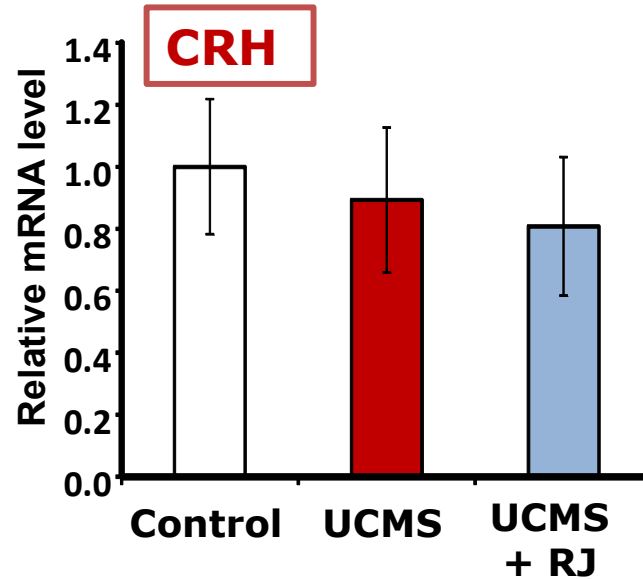
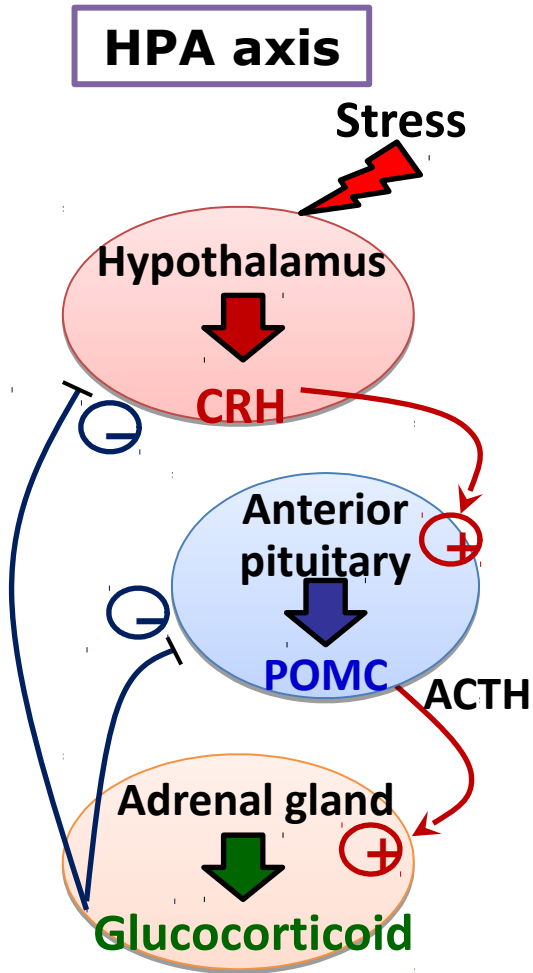
immobility time in tail suspension test, gene expression, microarray analysis

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 \pm SD

** P<0.01 vs. control by Steel test

CRH : corticotropin-releasing hormone
 POMC: pro-opiomelanocortin
 CORT : corticosterone

Microarray analysis of the adrenal gland

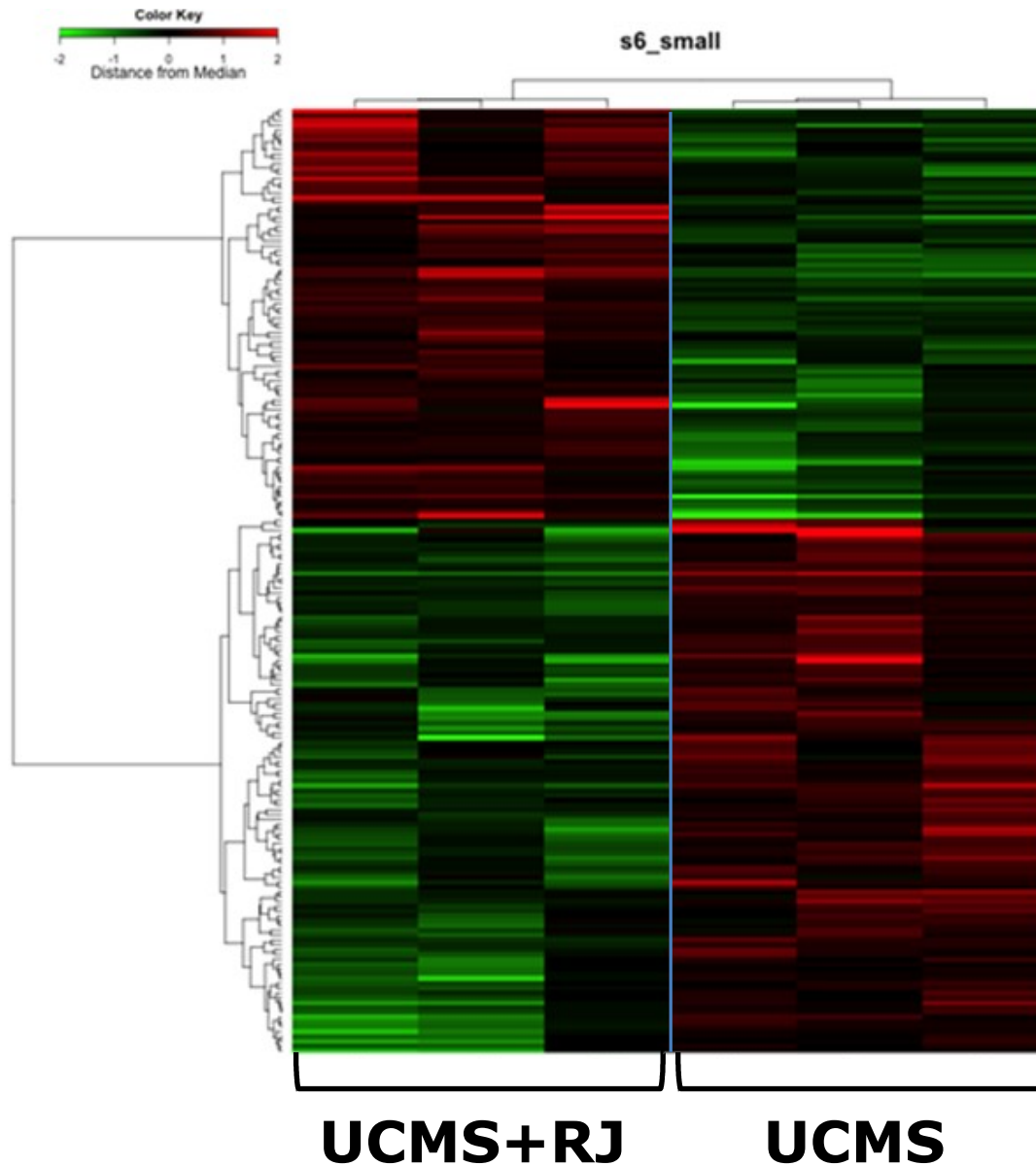
- Three representative animals in each group were used for microarray analysis of the adrenal glands.
- The number of changed genes
 - In the stressed group, 1158 genes changed compared with the control group.
 - In the RJ-fed, stressed group, 196 genes changed compared with the stressed group.

comparison

Control vs UCMS



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 contain

Steroid biosynthesis

Terpenoid backbone

Ubiquitin mediated proteolysis

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 (

PXR/RXR Activation

Heme Biosynthesis II

Tetrapyrrole Biosynthesis

LPS/IL-1 Mediated Inhibit

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.**

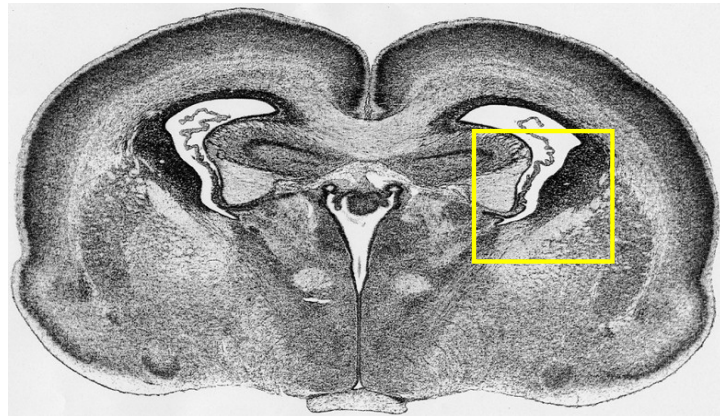
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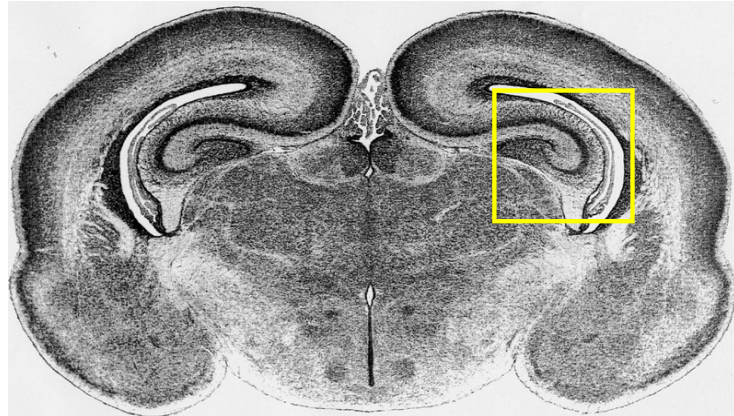
A hypothesis regarding the relationship of hippocampal neurons to depression

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.



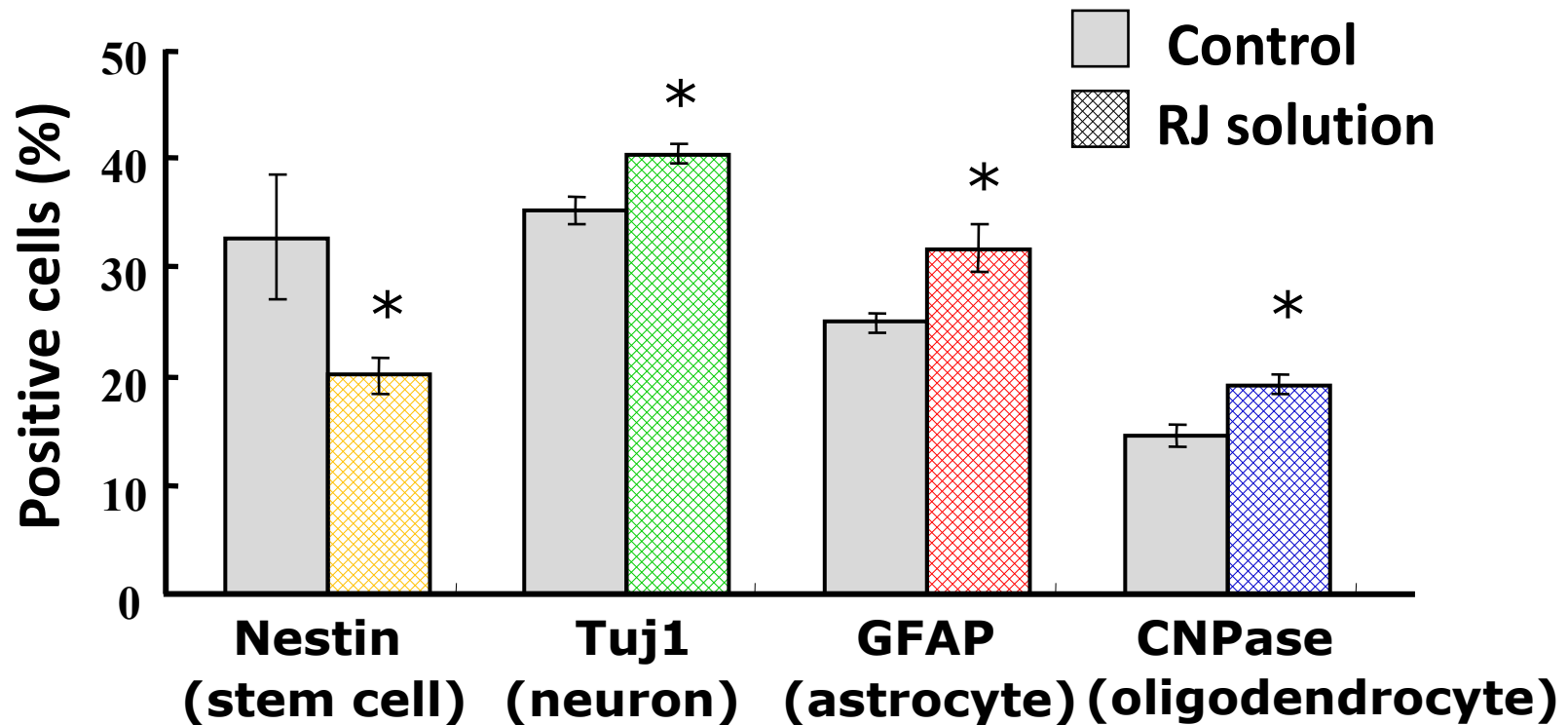
around the lateral ventricles



**granular cell layer of the
hippocampal dentate gyrus**

Effects of RJ on the differentiation of neural stem cells

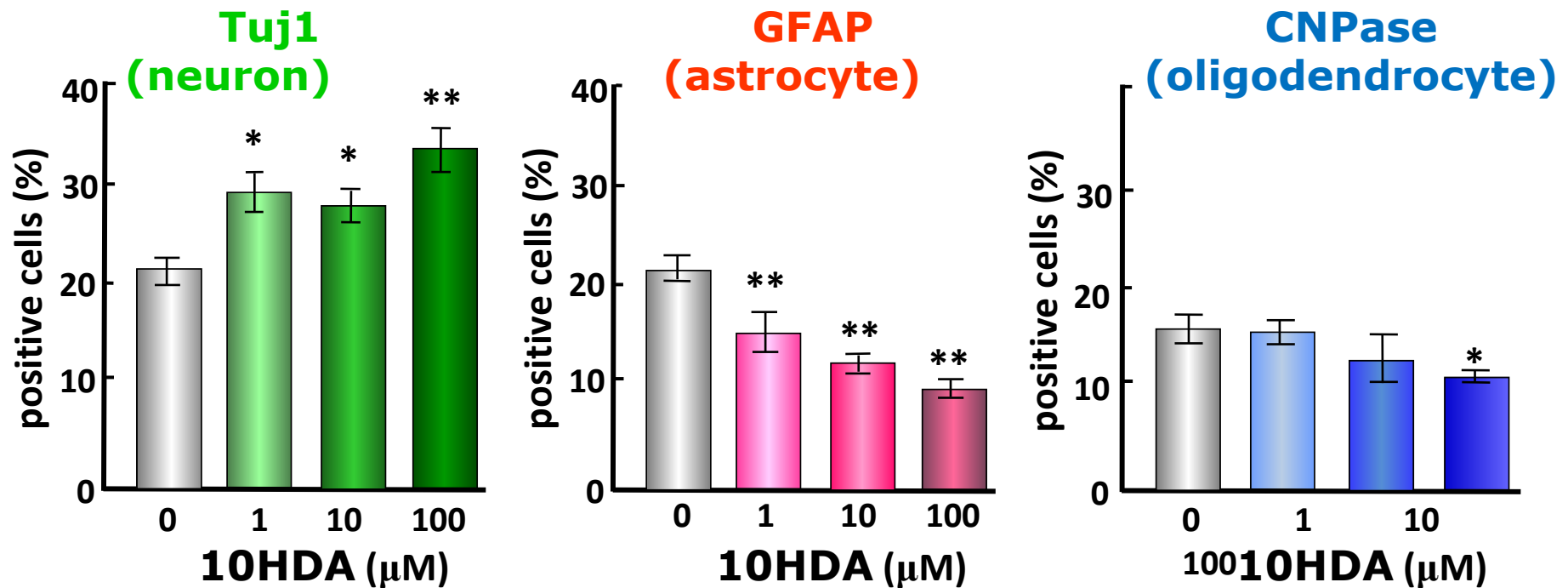
- RJ solution increased the rate of cells expressing neuron, astrocyte, and oligodendrocyte markers, and decreased that of undifferentiated cells.



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

Effects of 10HDA on the differentiation of neural stem cells

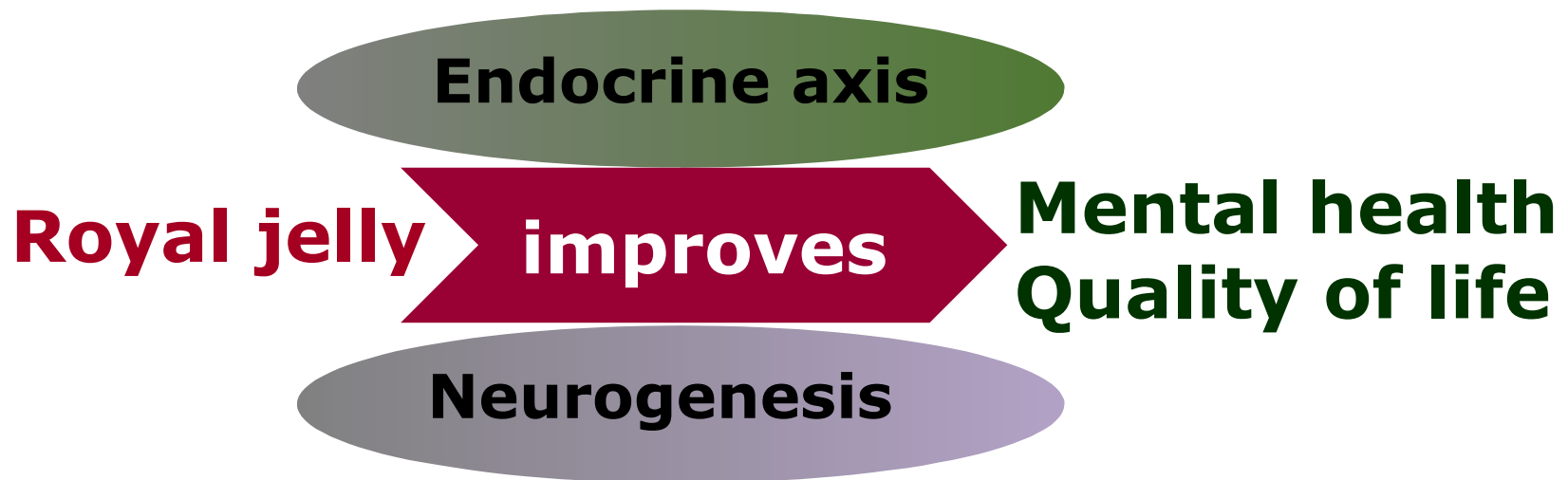
- 10-hydroxy-trans-2-decenoic acid (10HDA) increased the rate of cells expressing the neuronal marker Tuj1. 10HDA is thought to be one of the components of RJ for promoting neurogenesis.



*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



Nagaragawa Research Center, API Co., Ltd.