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Royal jelly ameliorates diet-induced obesity and glucose intolerance by promoting brown adipose tissue thermogenesis in mice

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Summary
Introduction: Identification of thermogenic food ingredients is potentially a useful strategy for the prevention of obesity and related metabolic disorders. It has been reported that royal jelly (RJ) supplementation improves insulin sensitivity; however, its impacts on energy expenditure and adiposity remain elusive. We investigated anti-obesity effects of RJ supplementation and their relation to physical activity levels and thermogenic capacities of brown (BAT) and white adipose tissue (WAT).
Methods: C57BL/6J mice were fed under four different experimental conditions for 17 weeks: normal diet (ND), high fat diet (HFD), HFD with 5% RJ, and HFD with 5% honey bee larva powder (BL). Spontaneous locomotor activity, hepatic triglyceride (TG) content, and blood parameters were examined. Gene and protein expressions of thermogenic uncoupling protein 1 (UCP1) and mitochondrial cytochrome c oxidase subunit IV (COX-IV) in BAT and WAT were investigated by qPCR and Western blotting analysis, respectively.
Results: Dietary RJ, but not BL, suppressed HFD-induced accumulations of WAT and hepatic TG without modifying food intake. Consistently, RJ improved hyperglycemia and the homeostasis model assessment-insulin resistance (HOMA-IR). Although dietary RJ and BL unchanged locomotor activity, gene and protein expressions of UCP1 and COX-IV in BAT were increased in the RJ group compared to the other experimental groups. Neither the RJ nor BL treatment induced browning of WAT.

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Conclusion: Our results indicate that dietary RJ ameliorates diet-induced obesity, hyperglycemia, and hepatic steatosis by promoting metabolic thermogenesis in BAT in mice. RJ may be a novel promising food ingredient to combat obesity and metabolic disorders.

Introduction

The pandemic of obesity has spurred a need for effective therapies to prevent and treat metabolic complications such as type 2 diabetes mellitus and nonalcoholic fatty liver disease. Although decreasing food intake and increasing physical activity constitute logical ways to tip energy balance toward weight loss, sustained interventions are rather difficult to achieve owing to poor adherence of lifestyle changes [1]. Identification of nutrients or food components, which are able to stimulate energy expenditure and thermogenesis, is potentially useful in developing strategies for the prevention and treatment of obesity and related metabolic disorders [2]. Previous findings that dietary supplementation of royal jelly (RJ), a honey bee product, improves oxidative stress, inflammation, lipid metabolism, and insulin sensitivity [3—5] suggest that this food component is a possible ingredient for preventing obesity-related metabolic disorders. However, effects of RJ on thermogenesis and adiposity have not been determined and thus mechanisms by which RJ ameliorates insulin resistance have not been fully understood.

Because the prevalence of brown adipose tissue (BAT) [6—8] and its contribution to sympathetically-activated nonshivering thermogenesis [9,10] have been widely appreciated in humans, increasing BAT thermogenesis may serve as a novel approach to modulate energy balance [11—13]. We and others previously reported that thermogenic food ingredients, i.e. capsaicin analogs (capsinoids) found in non-pungent type of hot pepper, increase energy expenditure through the activation of BAT thermogenesis in mice [14,15] and in humans [16,17]. Moreover, capsinoids and cold exposure ectopically induces brown-like (beige or brite) adipocyte formation in certain white fat depots through an increased half-life of PR domain containing 16 (PRDM16) [18], a dominant transcriptional regulator of brown/beige adipocyte development [19].

It is assumed that capsinoids act on transient receptor potential (TRP) channels on sensory neurons in the gastrointestinal tract and enhance efferent discharges of sympathetic nerves connecting to BAT, thereby increasing thermogenesis [14,20,21]. Considering a fact that hydroxydecenoic acid (HDEA) and hydroxydecanoic acid (HDAA), unique fatty acids in RJ, are capable to activate TRP channels [22], it seems conceivable that the beneficial effect of RJ on insulin sensitivity could be mediated by the activation of BAT and/or browning of WAT. To test this hypothesis, we examined the effects of dietary supplementation of RJ and honey bee larva (BL) which has similar nutritional composition to RJ but lacks HDEA and HDAA (Table 1), on thermogenic capacities of various adipose tissue and analyzed their relation to body fat-reducing effects. As BAT and beige fat thermogenesis is largely dependent on uncoupling respiration by mitochondrial uncoupling protein 1 (UCP1) [23—25], we assessed adipose thermogenic capacity by measuring expression levels of UCP1

Table 1 Amino acid composition of royal jelly (RJ) and bee larva (BL).

(g/100 g)	Lyophilized RJ	Lyophilized BL
Arginine	2.08	2.47
Lysine	3.50	3.29
Histidine	1.09	1.33
Phenylalanine	1.70	1.96
Tyrosine	1.66	2.42
Leucine	2.89	3.73
Isoleucine	1.84	2.27
Methionine	1.03	1.01
Valine	2.10	2.73
Alanine	1.21	2.64
Glycine	1.30	2.60
Proline	2.36	3.94
Glutamate	3.98	7.62
Serine	2.31	2.14
Threonine	1.72	1.90
Aspartate	6.88	4.47
Tryptophan	0.49	0.68
Cystine	0.40	0.48

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