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Letter to the Editor

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Quercetin Upregulates Uncoupling Protein 1 in White/Brown Adipose Tissues through Sympathetic Stimulation (J Obes Metab Syndr 2018;27:102-9)

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Quercetin is a naturally occurring polyphenolic flavonoid that is present in fruits and vegetables. A clinical study showed that increased intake of quercetin was associated with a reduced risk for developing cardiovascular diseases.[1] In an animal study, quercetin supplementation attenuated high-fat diet-induced adipose tissue expansion and upregulated energy expenditure, mitochondrial biogenesis, and the function and completeness of fatty acid oxidation.[2] In recent studies, quercetin induced the browning of 3T3-L1 white adipocytes[3] and produced a more brown-like phenotype, including higher mRNA expression of uncoupling protein 1 (UCP1).[4] Furthermore, quercetin has shown protective effects against obesity-induced inflammation and signs of metabolic dysregulation such as insulin resistance, hyperlipidemia, fatty liver, and muscle atrophy.[5-8] However, the underlying mechanisms of these actions have not been thoroughly investigated.

Choi et al.[9] demonstrated that dietary quercetin increased the level of UCP1 in the white and/or brown adipose tissue of high-fat diet-fed obese mice, accompanied by upregulated mRNA expression of thermogenesis-related genes, enhanced plasma norepinephrine level, and upregulated β-adrenergic receptor mRNA expression in white adipose tissue, along with AMP-activated protein kinase (AMPK) activation. Based on these results, the authors[9] concluded that quercetin upregulates UCP1 in white/brown adipose tissues through sympathetic stimulation, which was the title of their paper. Despite the significance of this study with respect to insight into quercetin-induced sympathetic stimulation, I have some concerns about this main conclusion, and additional points need further clarification.

First, the mechanism by which quercetin enhances the plasma norepinephrine level needs to be clarified. It is possible that the increased level of plasma norepinephrine was an incidental response to the stress condition of this experiment. Thus, Choi et al.[9] should rule out this possibility. Second, it is important to reveal how quercetin upregulates the β-adrenergic receptor mRNA level in the white adipose tissue. Third, even though quercetin may enhance the plasma norepinephrine level, it should be confirmed that the increased level of UCP1 in the white and/or brown adipose tissue is induced by direct effects of downstream of β-adrenergic receptor stimulation through experiments involving blockade of β-adrenergic receptor. It is possible that quercetin enhances the plasma norepinephrine level and/or increases the level of UCP1 in the white and/or brown adipose tissue by direct effects, independent of sympathetic stimu-

lation. AMPK/peroxisome proliferator-activated receptor gamma activation also may occur independent of sympathetic stimulation. A previous study in a cell model (3T3-L1 white adipocytes) indicated that the quercetin-associated browning effect[3] was not a result of sympathetic stimulation, and the effect was considered to be mediated in part by activation of AMPK.[3] Moreover, a clinical study showing that increased intake of quercetin is associated with a reduced risk for cardiovascular diseases[1] and other basic studies[2,3,5-7] demonstrating quercetin-induced increased UCP1 expression may be not related to sympathetic stimulation. Therefore, the title of this paper "Quercetin upregulates uncoupling protein 1 in white/brown adipose tissues through sympathetic stimulation" is not appropriate considering that this conclusion is not directly supported by Choi et al.'s data.[9]

In conclusion, future studies should focus on determining how quercetin enhances the plasma norepinephrine level and evaluate the direct activation of β-adrenergic receptor of white and/or brown adipose tissue by norepinephrine, independent of the direct effect of quercetin.

CONFLICTS OF INTEREST

The author declares no conflict of interest.

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