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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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Uncoupling protein 1 (UCP1) plays an important role in increasing energy expenditure and is considered as a new target for preventing obesity and metabolic complications. Quercetin elicits protective effects against obesity-induced peripheral/central inflammation and metabolic dysregulations.[1-4] Our previous study[5] showed that dietary quercetin supplementation increased the level of UCP1 in white adipose tissue (WAT) and/or brown adipose tissue (BAT) of high-fat diet (HFD)-fed obese mice and was accompanied by upregulated mRNA levels of thermogenesis-related genes. Quercetin supplementation enhanced the plasma norepinephrine level and tended to upregulate β3-adrenergic receptor mRNA level in the WAT of HFD-fed obese mice, accompanied by AMP-activated protein kinase (AMPK) activation. Subsequently, we showed that quercetin-induced UCP1 expression was blunted by a peroxisome proliferator-activated receptor gamma (PPARγ) antagonist in 3T3-L1 adipocytes. Based on these findings, we concluded that quercetin upregulated UCP1, leading to increased WAT browning and BAT activity, and the quercetin action was associated with activation of the AMPK/PPARγ pathway through norepinephrine-associated sympathetic stimulation.

We agree with the view that the quercetin action on UCP1 induction in the adipose tissue may involve other mechanisms independent of norepinephrine-associated sympathetic stimulation. As suggested, experiments using β-adrenergic receptor blocker may be helpful to confirm quercetin action through sympathetic stimulation in HFD-fed obese mice. A recent study has shown that quercetin-3-*O*-glucuronide, a major metabolite of quercetin, blocks norepinephrine-induced α2- and β2-adrenergic signals[6], which are responsible for cardiovascular effects such as increased heart rate and blood pressure. Interestingly, similar to β2-adrenegic receptor, stimulation of β3-adrenergic receptor increases the generation of cyclic AMP and the activation of protein kinase A; however, it is likely that β3-adrenergic receptor stimulation suppresses β2-adrenergic receptor over-activation in the myocardium.[7,8] Hence, it is tempting to speculate that quercetin may enhance UCP1 in the adipose tissues through norepinephrine-mediated β-adrenergic receptor activation without adverse cardiovascular effects. Further studies are needed to determine how quercetin enhances plasma norepinephrine and β3-adrenergic receptor mRNA in the adipose tissues, as well as the stress issue.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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