Prevention mechanism of hyperglycemia and insulin resistance by tea

Hitoshi Ashida

Department of Agrobioscience, Kobe University, Nada-ku, Kobe 657-8501, Japan.
Correspondent email: ashida@kobe-u.ac.jp

Summary

It is known that tea prevents hyperglycemia and insulin resistance. We show here that prevention mechanism of tea. In animal studies, green and black tea suppressed body weight gain and deposition of white adipose tissue in high-fat diet-fed mice. Increased expression of inflammatory cytokines, such as TNF-α and MCP-1 were decreased in adipose tissue of KK-A^y mice given tea. This would lead to prevention of insulin resistance. In muscle, tea improved hyperglycemia and glucose intolerance through stimulating glucose uptake activity accompanied by translocation of glucose transporter (GLUT) 4 to the plasma membrane. Moreover, tea retained the reduction of insulin receptor β-subunit, GLUT4 and AMP-activated protein kinase α in muscle of the high-fat diet-fed mice. In cultured cells, catechins suppressed differentiation of adipocytes, whereas stimulated GLUT4 translocation in muscle cells. It is, therefore, suggested that decreasing the expression of inflammatory cytokines in adipose tissue and regulation of the expression and translocation levels of GLUT4 in muscle cells are involved in the prevention mechanism of hyperglycemia and insulin resistance by tea.

Introduction

The health-promoting effects of tea, especially green tea, have been attributed to polyphenols, mainly catechins. For example, tea suppressed high-fat diet-evoked increases in body weight and adipose tissue weight (Nishiumi, *et al*. submitted). It has been reported that following phenomena are the actions of tea and its constituents: down-regulation of lipogenic enzymatic activity, up-regulation of lipolytic enzymatic activity, fat oxidation and thermogenesis in brown adipose tissue, regulation of the activity and expression of lipoproteins, and decreases in cell numbers of preadipocytes and adipocytes. Moreover, green, oolong and black tea have hypoglycemic effects. The mechanisms underlying the hypoglycemic effects of tea or tea constituents are the inhibition of digestive enzymes in the small intestine and gluconeogenic enzymes in the liver. Therefore, multiple mechanisms are concerned with the prevention of obesity, hyperglycemia and insulin resistance by tea. We elucidate our finding and possible mechanisms of tea or tea catechins in following section.

Results and discussion

Our previous report demonstrated that *ad libitum* drinking of green tea for 3 weeks to male Wistar rats fed a commercial chow decreased adipose tissue weight accompanying by the reduction of glucose uptake activity and the translocation of GLUT4 in adipose tissue, whereas this activity and GLUT4 translocation were increased in skeletal muscle (Ashida, *et al.*, 2004). To understand the decrease in the adiopose tissue weight, we investigated the differentiation of adipocytes using 3T3-L1 cells and found tea catechins, particularly Cg and EGC, suppressed the intracellular lipid accumulation and glycerol-3-phosphate dehydrogenase activity as differentiation markers through down-expression of PPARγ and C/EBPα, the master regulators for differentiation (Furuyashiki, *et al*., 2004). These results strongly suggest that down-expression of PPARγ and C/EBPα will be involved in the prevention of fat deposition to adipose tissue *in vivo*. Indeed, we observed down-regulation of PPARγ. expression in normal rats given green tea (Ashida, *et al.*, 2004).

Reduction of glucose uptake activity and the translocation of GLUT4 in adipose tissue is another possibility for the anti-obesity effect of tea. Not only green tea extract but also oolong and black tea extracts suppressed insulin-induced glucose uptake in 3T3-L1 adipocytes (Furuyashiki, *et al*., 2003). Our recent report demonstrated that gallate-type catechins specifically suppressed insulin-induced

glucose uptake, whereas non-gallate-type catechins increased the uptake in the absence of insulin in 3T3-L1 adipocytes (Ueda, *et al*., 2010). Cg and EGCg decreased phosphorylation of PKCλ/ζ in the presence of insulin without affecting insulin-induced phosphorylation of IR and Akt. These results indicated that gallate-type catechins strongly contribute to the decrease in the insulin-induced glucose uptake by tea through activation of atypical PKC and its downstream events of GLUT4 translocation.

Muscle is a main target for prevention of hyperglycemia and diabetes mellitus, because consumption of postprandial blood glucose in muscle can account for over 70%. As mentioned above, intake of green tea increased glucose uptake and GLUT4 translocation in skeletal muscle (Ashida, *et al*., 2004). The same effect was observed in normal and insulin-resistant L6 myotubes treated with 1 nM EGCg and in muscle of mice dosed with 75 mg EGCg (Ueda, *et al*., 2008). Moreover, our recent results demonstrated that tea retained down-expression of insulin receptor β-subunit, GLUT4 and AMP-activated protein kinase α in muscle of high-fat diet-fed mice. As a mechanism, tea decreased production of inflammatory cytokines, such as TNF-α and MCP-1, which are induced by a long-term intake of high-fat diet, from adipose tissue (Imada, *et al*., unpublished data).

Taken together our results, tea and tea catechins prevent obesity through suppression of differentiation of adipocytes. This effect leads to lower the production of inflammatory cytokines by the high-fat diet. Moreover, tea catechins modulate glucose transport system in skeletal muscle and adipose tissue independent on the insulin signaling pathway. These effects are additively or synergistically acted for the prevention of hyperglycemia and diabetes mellitus.

Acknowledgements

Part of this study was supported by Creation of Innovation Centers for Advanced Interdisciplinary Research Areas in Special Coordination Funds for Promoting Science and Technology Program by MEXT, Japan.

References

Ashida, H., Furuyashiki, T., Nagayasu, H., Bessho, H., Sakakibara, H., Hashimoto, T., and Kanazawa, K. (2004) Anti-obesity actions of green tea: possible involvements in modulation of the glucose uptake system and suppression of the adipogenesis-related transcription factors. Biofactors 22: 135-140.

Furuyashiki, T., Terashima, S., Nagayasu, H., Kaneko, A., Sakane, I., Kakuda, T., Kanazawa, K., Danno, G., and Ashida, H. (2003) Tea extracts modulate a glucose transport system in 3T3-L1 adipocytes. In "Food Factors in Health Promotion and Disease Prevention" eds. by Fereidoon Shahidi, Chi-Tang Ho, Shaw Watanabe, and Toshihiko Osawa, American Chemical Society, Washington D.C., pp. 224-234.

Furuyashiki, T., Nagayasu, H., Aoki, Y., Bessho, H., Hashimoto, T., Kanazawa, K., and Ashida, H. (2004) Tea catechin suppresses adipocyte differentiation accompanied by down-regulation of PPARγ2 and C/EBPα in 3T3-L1 cells. Biosci. Biotechnol. Biochem. 68: 2353-2359.

Nishiumi, S., Bessyo, H., Kubo, M., Aoki, Y., Tanaka, A., Yoshida, K., and Ashida, H. (Submitted) Green and black tea suppress hyperglycemia and insulin resistance by retaining the expression of glucose transporter 4 in muscle of high-fat diet-fed C57BL/6J mice.

Ueda, M., Nishiumi, S., Nagayasu, H., Fukuda, I., Yoshida, K., and Ashida, H. (2008) Epigallocatechin gallate promotes GLUT4 translocation in skeletal muscle. Biochem. Biophys. Res. Commun. 377: 286-290.

Ueda, M., Furuyashiki, T., Yamada, K., Aoki, Y., Sakane, I., Fukuda, I., Yoshida, K., and Ashida, H. (2010) Tea catechins modulate the glucose transport system in 3T3-L1 adipocytes. Food Function 2: in press.