Intake of tea prevents postprandial hyperglycemia by promoting GLUT4 translocation in skeletal muscle

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Summary

The anti-hyperglycemic effects of tea are well documented. However, the effects of tea on the translocation of glucose transporter 4 (GLUT4), the major glucose transporter for glucose uptake in the postprandial period, in skeletal muscle and the underlying molecular mechanisms are not fully understood. In this study, we investigated the translocation of GLUT4 and its related signaling pathways in skeletal muscle of animals given fermented tea. In long-term feeding experiment, green and black tea improved postprandial hyperglycemia by stimulating glucose uptake activity accompanied by the translocation of GLUT4 to the plasma membrane in muscle of high-fat diet-fed mice. In short-term feeding experiment, oolong, black and pu-erh tea activates both PI3K/Akt- and AMPK-dependent signaling pathways to induce GLUT4 translocation, and increases the expression of insulin receptor to improve glucose intolerance. In conclusion, tea may prevent hyperglycemia and diabetes mellitus by promoting glucose uptake accompanying with GLUT4 translocation in muscle. Both PI3K/Akt- and AMPK-dependent signaling pathways are involved in the tea-induced GLUT4 translocation.

Introduction

Type 2 diabetes mellitus is characterized by the loss of sensitivity to insulin, and the pathogenesis of type 2 diabetes mellitus involves the progressive development of insulin resistance in peripheral tissues. Therefore, preventing excess postprandial hyperglycemia and improving insulin resistance are effective strategies to treat hyperglycemia and diabetes mellitus. Glucose transporters (GLUTs) play an important role in the regulation of blood glucose levels. GLUT4 is specifically expressed in skeletal muscle and adipose tissue, where it takes up glucose to reduce postprandial hyperglycemia. GLUT4 is mainly localized in intracellular storage vesicles and translocates to the plasma membrane in response to insulin. The insulin and AMP-activated protein kinase (AMPK) signaling pathways are the major regulators of GLUT4 translocation in muscle.

The anti-hyperglycemic effects of tea are well documented. Tea and its components were reported to inhibit digestive enzymes in the small intestine (Li *et al*.) and gluconeogenic enzymes in the liver (Abe *et al.*). Recent studies have focused on insulin-sensitive glucose transporter 4 (GLUT4) as a novel target of food factors (Nishiumi, et al., Ueda, et al., Yamashita et al. 2012a). Previously, we demonstrated that ad libitum drinking of green tea increased skeletal muscle glucose uptake and GLUT4 translocation in male Wistar rats (Ashida et al.). However, it is unclear whether tea prevents loss of the protein level of insulin receptor (IR) and GLUT4 under the insulin resistant conditions. Moreover, the effects of fermented tea on the translocation of GLUT4 in skeletal muscle and its underlying molecular mechanism are not fully understood. Therefore, in this study, we investigated whether tea improves hyperglycemia and insulin resistance by modulating the function and expression of GLUT4 in diet-induced diabetes model animals, and the effects of tea on GLUT4 translocation and its related signaling pathways in normal animals.

Materials and methods

Animal experiments were carried out according to the ‘Guidelines for the Care and Use of Experimental Animals’ at Kobe University Rokkodai Campus. For the diet-induced diabetes model experiment, Male C57BL/6J mice (4 weeks old) were a high-fat diet containing 29% lard or an AIN93M-based control diet for 14 weeks with green tea, black tea or water,. For the mechanism of tea-induced GLUT4 translocation, Male

ICR mice (6 weeks old) were given free access to a commercial chow with oolong tea, black tea, pu-erh tea, or water for 7 days. Assessment of glucose tolerance was performed by the oral glucose tolerance test. GLUT4 translocation and phosphorylation of its related signaling pathways were estimated by western blot.

Results and discussion

As the results from diet-induced diabetes model experiment, both teas suppressed body weight gain and deposition of white adipose tissue caused by the diet. In addition, they improved hyperglycemia and glucose intolerance by stimulating glucose uptake activity accompanied by the translocation of glucose transporter (GLUT) 4 to the plasma membrane in muscle. Long-term consumption of the high-fat diet reduced levels of IR, GLUT4 and AMPK in muscle, and green and black tea suppressed these decreases. These results strongly suggest that green and black tea suppress high-fat diet-evoked hyperglycemia and insulin resistance by retaining the level of GLUT4 and increasing the level of GLUT4 on the plasma membrane in muscle.

Next, we investigated that the translocation of GLUT4 and its related signaling pathways in skeletal muscle of male ICR mice given fermented tea for 7 days. Intake of oolong, black, or pu-erh tea enhanced GLUT4 translocation to the plasma membrane of skeletal muscle (Fig.1). Each type of fermented tea stimulated the phosphorylation of phosphoinositide 3-kinase (PI3K), Akt/protein kinase B, and AMPK. Fermented tea also increased the protein expression of IR. These results strongly suggest that fermented tea activates both PI3K/Akt- and AMPK-dependent signaling pathways to induce GLUT4 translocation and increases the expression of IR to improve glucose intolerance.

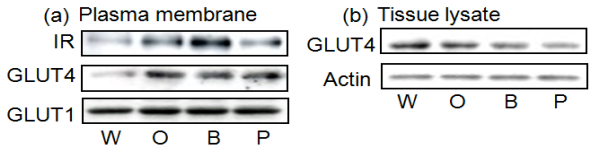

Fig. 1 Effects of fermented tea on GLUT4 translocation in skeletal muscle of mice. W; water, O; oolong tea, B; black tea, and P; pu-erh. (Yamashita *et al*. 2012b)

Taken together, these results indicate that tea suppresses high-fat diet-induced hyperglycemia and insulin resistance by maintaining GLUT4 expression and increasing its translocation to the plasma membrane in skeletal muscle. Both PI3K/Akt- and AMPK-signaling pathways are deeply involved in the tea-induced GLUT4 translocation. Moreover, intake of tea may increase IR expression by unknown mechanism. In conclusion, tea may improve hyperglycemia and insulin resistance by modulating the function and expression of GLUT4 and its related proteins.

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