Insulin mimetics are considered as prospective antidiabetic agents, and the disaccharide, neohesperidose, has been found to show insulin mimetic activity against L6 cells. We screened several other disaccharides for their insulin mimetic activity and identified three new insulin mimetic disaccharides.

Key words: insulin mimic; disaccharide; diabetes mellitus; glucose uptake; L6 cell

Glucose homeostasis is maintained by multiple hormones with some adverse effects. Elevation of the blood sugar level is handled together by several hormones, but lowering of the elevated blood sugar level is handled by the peptide hormone insulin alone. Defective insulin secretion or a decrease of its sensitivity easily leads to impaired control of the blood sugar level to the status called diabetes mellitus. Regulating the blood sugar level is the most important action in the medical treatment of diabetes mellitus, as a high level of blood sugar eventually leads to problems like cardiovascular disease, renal failure, blindness and neurological disorders.1) The response after dining, the main factor that rapidly elevates the blood sugar level, is especially important. Exogenous insulin is currently employed as a medicine for this purpose to maintain the blood sugar level of patients.2,3) However, the physical instability of insulin due to its peptidic nature restricts its use to only by injection. The development of an alternative agent with more stable characteristics, which can be used orally, would give patients of diabetes mellitus a choice for treating their disease.

Natural products have been widely studied as a source of agents for blood sugar control, and several plants are utilized as an easily applicable supplementary food. Several natural products like flavonoids have been reported as insulin mimetic compounds, although most of these are known to work as a peroxisomal proliferator activated receptor (PPAR) agonist and do not exactly mimic the activity of insulin.4,5) Other than those PPAR agonists, a complex of flavonoids and an inorganic metal has been reported to resemble the action of insulin.6–8) We have recently studied an organic compound having insulin mimetic activity.9) This compound, neohesperidose (1), is a disaccharide composed of D-glucose and L-rhamnose and was found to be active in the principle of the insulin mimetic flavonoid glycoside, kaempferol 3-O-neohesperidoside. Treating muscle model L6 cells with neohesperidose (1) at a concentration in the sub-nanomolar range stimulated the cells to rapidly uptake glucose just as if stimulated by insulin. The simple and stable characteristics of 1 provide an opportunity to utilize it as an insulin alternative, although the maximum uptake of glucose induced by 1 was relatively low compared with the effect of insulin. We presumed that several other disaccharides may exhibit the same activity and selected in this study several disaccharides to investigate their insulin mimetic activity.

Our first choices were disaccharides connected through the β1→4 bond, as this is one of the most common glycosidic bonds seen in natural products. Cellobiose (2), β-D-glucose-(1→4)-D-mannose (3), β-D-mannose-(1→4)-D-glucose (4), β-D-mannose-(1→4)-D-mannose (5), lactose (β-D-galactose-(1→4)-D-glucose) (6) and epilactose (β-D-galactose-(1→4)-D-mannose) (7) were tested for their activity,10) but all failed to induce insulin mimetic activity (data not shown). We then investigated compounds with various types of glycosidic bond. Di-glucose isomers (2 and 8–15) with most of the possible ideal structures were selected and tested. Three of these tested disaccharides, trehalose (8), isomaltose (12) and gentiobiose (15), showed...
insulin mimetic activity against L6 cells, respectively inducing 130%, 136% and 132% increases in 2-deoxyglucose (2-DG) uptake compared to control (Fig. 1). The other disaccharides seemed to slightly elevate the 2-DG uptake, but not significantly more than the control. The structure of these active disaccharides varies in detail, and some restriction to the position of the glycosidic bond seems to be relevant, and we can point out that the 1,4-disaccharide had no activity recognizable from the results for compounds 2–7 and 11. Other structural rules are not apparent among the three active disaccharides or with the previously found insulin mimetic disaccharide, neohesperidose (1), except for them all being disaccharides. However, the results obtained here provide an opportunity to find additional active disaccharides. Our initial objective to find some disaccharides having insulin mimetic activity has been accomplished.

In conclusion, we investigated three new insulin mimetic disaccharides. Although none of these compounds (8, 12 and 15) induced higher activity than neohesperidose (1), and the common glycosidic bond of these compound seemed to have low tolerance under digestive conditions, the results obtained here showed the possibility of several disaccharides working as an insulin mimetic. Further studies on insulin mimetic disaccharides should give an opportunity to use them as a chemical treatment against diabetes mellitus.

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References and Notes

10) Insulin mimetic activity assay was performed as written in reference 9.
11) Commercial products were used without further purification. Compounds 2, 8–12 (>98%) were purchased from Wako Pure Chem. Ind., Ltd., 13 (>98%) was purchased from Carbosynth Ltd., 14 (>97%) was purchased from Seikagaku Biobusiness Co., 15 (>96%) was purchased from Tokyo Chem. Ind., Co., Ltd.