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Requirement of the Glycosyl Parts in Platycodin D to Stimulate Pancreatic Exocrine Secretion

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Abstract: The whole structure of platycodin D is found to be essential to stimulate the volumetric increase in the pancreatic exocrine secretion, while the prosapogenins prepared from platycodin D increased only protein output of pancreatic juice.

Pancreatitis is one of the most inveterate diseases, and Foipan@ (camostat mesilate) which inhibits pancreatic proteases is a popular medicine on a clinical level. The treatment using Foipan@ is very effective for acute pancreatitis by protecting pancreatic tissues from autodigestion, however, it is not commonly effective for chronic pancreatitis. One of us, Taguchi, found that a "kampo" remedy, "Kikyo-to", the decoction of dried roots of *Platycodon grandiflorum* and *Glycyrrhiza uralensis*, decreased the symptom of chronic pancreatitis, *e.g.* diarrhea with stinging pain on the side of the stomach.[1] We reported in the previous paper, platycodin D (**1**)[2] is an active component in Kikyo-to for the chronic pancreatitis.[3] Here, we would like to report the study on the effects of the glycosyl parts in **1** and its related compounds on the pancreatic exocrine secretion.

Platycodin D_2 (**2**), D_3 (**3**), and desapio-platycodin D (**4**), isolated as the minor components from *Platycodon grandiflorum* roots during the purification of **1** were first assayed according to the method in the literature.[3] Platycodin D_2 (**2**) and D_3 (**3**) which have an additional glucose on the glucose unit of **1** increased only in the protein output of pancreatic juice, while **1** stimulated both volumetric increase and protein output in pancreatic exocrine secretion (Fig. 1). Desapio-platycodin D (**4**), which lacks the apiose at the non-reducing terminal of C-28 oligosaccharide of **1**, more potently stimulated the total protein output than **1**, however, it showed just a slight volumetric increase in the exocreation. The results obtained so far suggested that both the non-modified glucose and the apiose units of **1** were essential to stimulate the volumetric increase in pancreatic juice, and these two sugar units were not related to protein output so much. Since it is known that the volumetric increase in pancreatic juice secretion removes abdominal pain of the chronic pancreatitis patients, the contribution of the glucose and the apiose units of **1** to the activity was next scrutinized. Desgluco-platycodin D (**5**), platycodigenin 3-*O*-β-D-glucopyranoside (**6**), and methyl β-D-apiofuranosyl(1→3)-β-D-xylopyranosyl(1→4)-α-L-rhamnopyranosyl(1→2)-L-arabinopyranoside (**7**) were prepared for this purpose, as follows. The ester glycosyl

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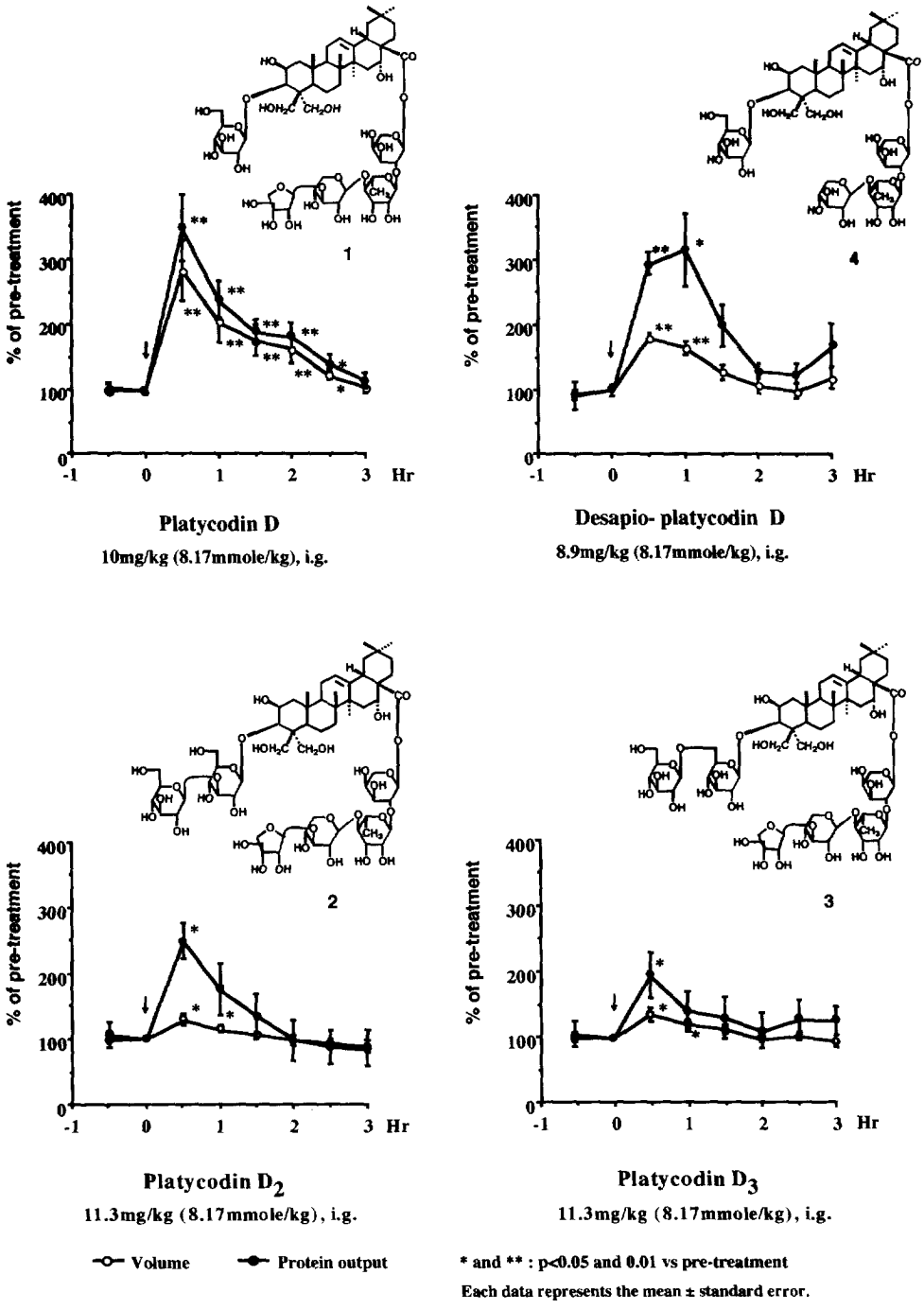

Fig.1 Effects of Platycodin D, D_2, D_3 and Desapio-platycodin D on pancreatic exocrine secretion in conscious rats

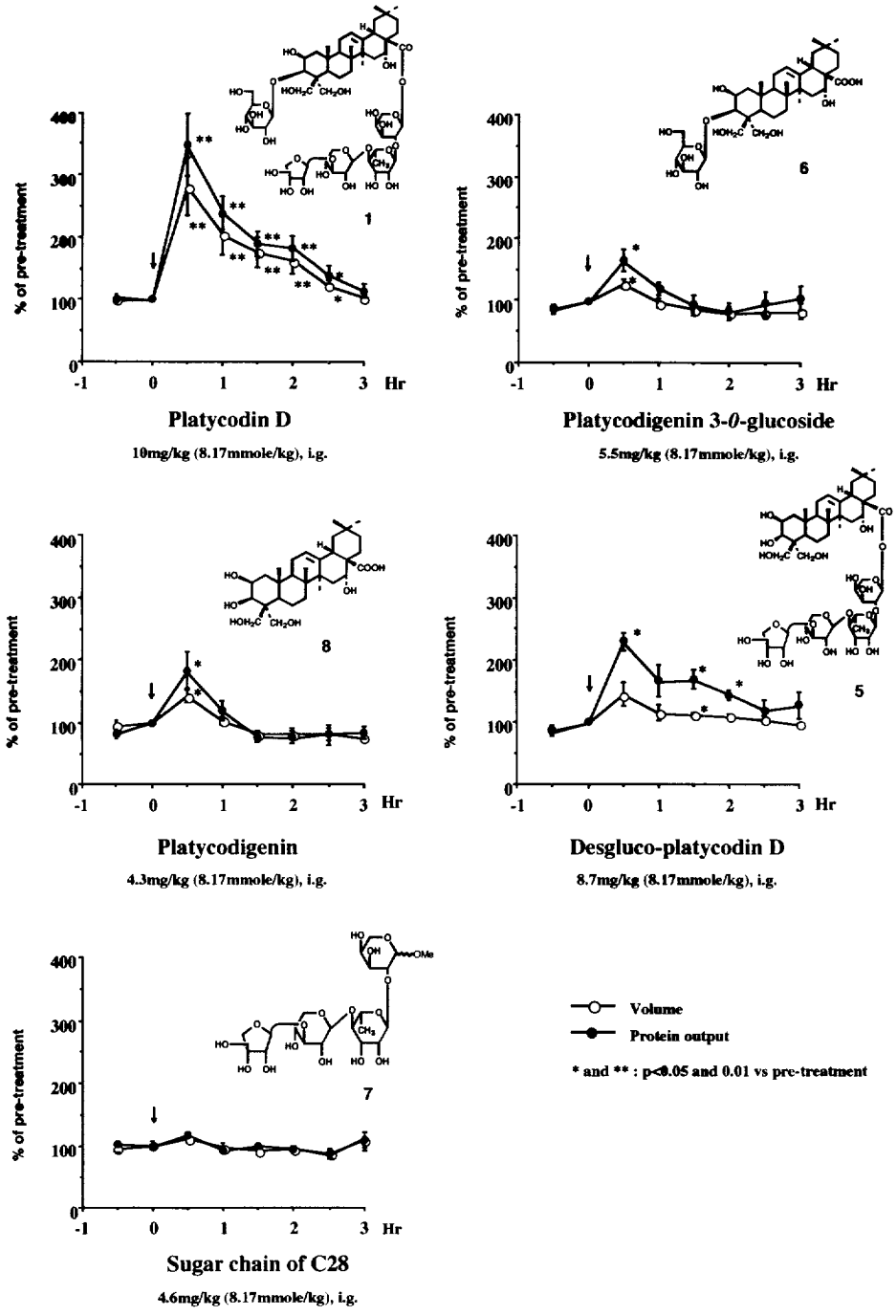

Fig.2 Effects of partial hydrolysates of Platycodin D on pancreatic exocrine section in conscious rats

bond of platycodin D (**1**) was cleaved with potassium iodide in the presence of allyl alcohol and 2,6-luthidine at 120 °C for 5 hours to give allyl β-D-apiofuranosyl(1→3)-β-D-xylopyranosyl(1→4)-α-L-rhamnopyranosyl(1→2) arabinopyranoside (51%) and **6** (72%).[4] The similar reaction replaced allyl alcohol with methanol afforded **7**,[5] and platycodigenin (**8**) was easily obtained by the acid treatment of **6**. Acetylation of allyl β-D-apiofuranosyl (1→3)-β-D-xylopyranosyl(1→4)-α-L-rhamnopyranosyl(1→2)arabinopyranoside with acetic anhydride and pyridine gave the nonaacetate, of which allyl group was cleaved with $(Ph_3P)_4Pd$ in acetic acid.[6] Without any purification, the obtained residue was derived to β-D-apiofuranosyl(1→3)-β-D-xylopyranosyl(1→4)α-L-rhamnopyranosyl (1→2)arabinopyranosyl trichloroimidate nonaacetate with trichloroacetonitrile in the presence of diazabicyclo-undecene (DBU) (96% in 3 steps).[7] The glycosylation of platycodigenin pentaacetate with the trichloroimidate was attained by Schmidt method using boron trifluoride etherate ($BF_3 \cdot Et_2O$) as the activating reagent to afforded the peracetate of **5** (77%).[8] Careful deacetylation of the peracetate with 0.1N NaOH afforded **5** (85%).[9]

Since the artificial derivatives (**5**, **6**, **7**, and **8**) of platycodin D were obtained as mentioned above, the effects to the pancreatic exocrine secretion in concious rats were measured.[3] None of the derivatives (**4**, **5**, **6**, **7**, and **8**), which have the partial structures of **1**, exhibited the volumetric increase in the secretion of pancreatic juice while compound **5** as well as **4** showed the slightly continued increase in the protein output (Fig. 2).

We concluded that the whole structure of **1** having two sugar units (apiose and β-D-glucopyranose) is requisite to stimulate the volumetric increase in the pancreatic exocrine secretion, although both **4** and **5** which lack either apiose or β-D-glucopyranose stimulated the protein output.

The transformation of the aglycon part and the study on the stimulation activity to the pancreatic exocrine secretion are in progress.

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References and Notes

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9. ^{13}C-NMR (in C_5D_5N) δ : 45.4 (C-1), 71.9 (C-2), 76.1 (C-3), 47.6 (C-4), 48.6 (C-5), 19.8 (C-6), 34.3 (C-7), 41.0 (C-8), 50.4 (C-9), 37.7 (C-10), 24.7 (C-11), 123.3 (C-12), 144.8 (C-13), 42.8 (C-14), 36.4 (C-15), 74.5 (C-16), 50.1 (C-17), 42.0 (C-18), 47.3 (C-19), 31.2 (C-20), 36.7 (C-21), 31.8 (C-22), 64.7 (C-23), 66.6 (C-24), 18.0 (C-25), 17.9 (C-26), 27.6 (C-27), 176.2 (C-28), 33.4 (C-29), 25.6 (C-30), 94.1 (Ara-1), 76.2 (Ara-2), 70.7 (Ara-3), 66.4 (Ara-4), 63.5 (Ara-5), 101.6 (Rha-1), 72.5 (Rha-2), 72.9 (Rha-3), 84.1 (Rha-4), 69.0 (Rha-5), 18.5 (Rha-6), 107.1 (Xyl-1), 75.4 (Xyl-2), 86.0 (Xyl-3), 69.9 (Xyl-4), 67.3 (Xyl-5), 111.7 (Api-1), 78.3 (Api-2), 80.4 (Api-3), 75.4 (Api-4), 66.2 (Api-5).