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Preliminary Report

Acarbose attenuates postprandial hyperlipidemia: investigation in an intestinal absorptive cell model

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Acarbose is an α-glucosidase inhibitor that reduces postprandial hyperglycemia [1]. Long-term treatment with acarbose also decreases serum total cholesterol and triglycerides in diabetic patients, probably because acarbose improves insulin resistance and therefore suppresses lipolysis in the peripheral adipose tissue and synthesis of very low-density lipoprotein (VLDL) [2]. Interestingly, 2 groups have reported that acute administration of acarbose also improves postprandial hyperlipidemia, a risk factor for cardiovascular disease. Kado et al [3] found that administration of acarbose reduced the level of remnant-like particle lipoproteins, which contain apolipoprotein (apo) B-48. Moreover, Ogawa et al [4] reported that acute administration of acarbose to humans reduced postprandial triglyceride and chylomicron levels without changing VLDL. These findings suggest a possible direct effect of acarbose on the absorption of lipids from the small intestine [3-5], but the underlying mechanism has not been elucidated. Accordingly, we examined the effect of acarbose on Caco-2 cells, a common in vitro model of enterocytes. Fatty acid absorption by Caco-2 cells was examined by using lipid micelles containing ^{3}H-labeled oleic acid [6]. Briefly, Caco-2 cells were differentiated into enterocyte-like cells by growth on filters, after which lipid micelles were added to the apical medium and incubation was done for 24 hours. Afterward, triglyceride-rich lipoproteins were harvested from the basolateral medium by ultracentrifugation [6]. The apo B-48 level was determined with a commercial assay (apo B-48 CLEIA Fujirebio kit; Fujirebio, Tokyo, Japan), and apo A-I was measured by an enzyme-linked immunosorbent assay [7]. Lipoproteins secreted into the basolateral medium were analyzed by high-performance liquid chromatography (LipoSEARCH System; Skylight Biotech, Tokyo, Japan). Data are shown as the mean ± SEM. Each assay was performed in triplicate unless otherwise indicated. For parametric data, mean values were compared by Student *t* test. For nonparametric data, the Mann-Whitney *U* test was used.

Exposure of Caco-2 cells to acarbose at a concentration of 10 mmol/L reduced oleic acid absorption by 30%, triglyceride-rich lipoprotein secretion by around 10%, and apo B-48 secretion by 50%, whereas apo A-I secretion was not affected (Fig. 1). Acarbose showed no toxicity for cultured Caco-2 cells as determined by lactate dehydrogenase release (data not shown).

Although such reductions were detected at a high dose of acarbose, specific inhibition of apo B-48 production over apo A-I production in Caco-2 cells suggests that this drug could reduce chylomicron synthesis or secretion by intestinal absorptive cells, a result that is consistent with earlier findings in humans [3-5]. On the other hand, acarbose had little effect on triglyceride-rich lipoprotein secretion. This may be because more than half of the triglyceride-rich lipoproteins secreted by Caco-2 cells are carried by apo B-100,

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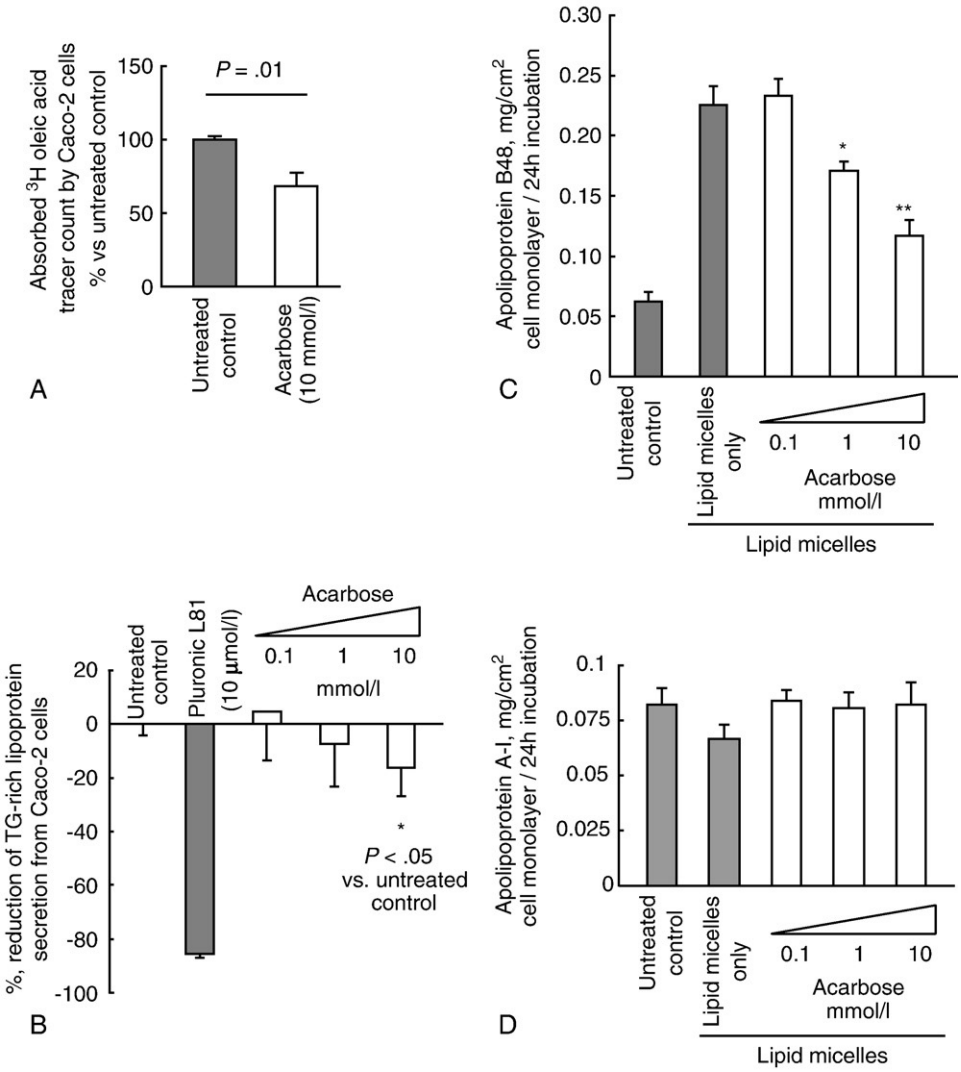

Fig. 1. A, Acarbose reduces oleic acid absorption by Caco-2 cells. Caco-2 cells were incubated for 24 hours with ^{3}H-oleic acid–containing lipid micelles in the presence (open bar) or absence (gray bar) of 10 mmol/L acarbose in the apical medium. Afterward, the residual tracer was measured. Mean and SEM of n = 3 assays. B, Acarbose reduces triglyceride-rich lipoprotein secretion by Caco-2 cells. The tracer count in the lipoprotein fraction obtained from the basolateral medium by a PD-10 gel filtration was almost reduced to zero in the presence of pluronic L81, a chylomicron synthesis inhibitor, confirming that this fraction contained triglyceride-rich lipoproteins. Addition of 10 mmol/L acarbose reduced triglyceride-rich lipoprotein secretion by approximately 10%. Mean and SEM of n = 3 assays. C and D, Acarbose reduced apo B-48 secretion by Caco-2 cells, but not apo A-I secretion. Mean and SEM of n = 3 assays.

a constituent of VLDL [6]. However, it remains uncertain whether acarbose has a specific effect on lipid absorption and/or trafficking. Alternatively, the presence of acarbose or inhibition of glucose absorption in the small intestine may generate changes in the intestinal lumen that disturb the physiologic environment required for effective lipid absorption, such as alterations of ion transport or acidity. Remnant-like lipoprotein particles are potent atherogenic lipoproteins that originate from the small intestine and are carried by apo B-48. Accordingly, an effect of acarbose on postprandial lipid metabolism like that indicated in this study could contribute to the reduced risk of cardiovascular events during treatment with this drug.

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