Glucagon-like peptide-1(7–36) amide and glycogen synthesis in the liver

Dear Sir,

Glucagon like-peptide-1 (GLP-1) (7–36) amide/(7–37) is an intestinal post-translational product of proglucagon and stimulates insulin secretion in a glucose-dependent manner [1]. In addition, GLP-1 (7–36) amide/(7–37) suppresses glucagon secretion and stimulates somatostatin secretion [2]. As for its extrapancreatic effects, it has been suggested that GLP-1 (7–36) amide directly promotes glucose uptake in human in vivo studies [3, 4]. GLP-1 receptor gene is expressed with relatively high abundance in the pancreatic islet, lung and stomach, and also expressed at a lower level in the brain, liver, skeletal muscle and kidney [5]. However, our previous study demonstrated that GLP-1 (7–37) does not affect glucose output from the perfused rat liver [6], and it did not block any of the actions of glucagon in isolated rat hepatocytes [7]. Valverde et al. [8] however, recently demonstrated that both GLP-1 (7–36) amide and GLP-1 (1–36) amide stimulate the incorporation of D-[U-¹⁴C] glucose into glycogen in isolated rat hepatocytes with a higher potency than insulin. We therefore examined the effect of GLP-1 (7–36) amide on glycogen

synthesis in rat hepatocytes using the same methods as those of Valverde et al. [8] except for the preincubation periods of isolated hepatocytes.

In our study, insulin increased the rate of incorporation of D-[U-¹⁴C] glucose into hepatocyte glycogen in dose-dependent manner at concentrations between 10^{-10} and 10^{-8} mol/l (Fig. 1). The maximal increment of the rate of glucose incorporation by insulin was 250.8 ± 13.1 % of the control experiment (addition of vehicle) at 10^{-8} mol/l. On the other hand, GLP-1 (7–36) amide did not affect the rate of glucose incorporation at concentrations ranging from 10^{-12} mol/l to 10^{-7} mol/l (Fig. 1). Glucagon at 10^{-9} mol/l suppressed the incorporation of glucose into glycogen (52.3 ± 6.4 % of control) and the combination of 10^{-9} mol/l insulin and 10^{-9} mol/l glucagon inhibited each action (100.4 ± 10.1 % of control). The rate of incorporation with both 10^{-8} mol/l GLP-1 (7–36) amide and 10^{-9} mol/l glucagon tended to decrease less than with 10^{-8} mol/l glucagon alone (43.3 ± 8.6 % of control vs 52.3 ± 6.4 %, $p < 0.1$).

We could not demonstrate any insulin-like effects of GLP-1 (7–36) amide on glucose metabolism in isolated rat hepatocytes, although insulin stimulated the glucose incorporation more remarkably than in the experiments by Valverde et al. [8]. It was rather suggested that GLP-1 (7–36) amide might suppress the glucose incorporation into glycogen in cooperation with glucagon. A marked difference in experimental methods is the culture time of the cells; they used the cells immediately after the isolation, but we incubated the cells for 24 h. We therefore also performed the study using freshly isolated hepatocytes. The results, however, were the same (data not shown). Although a potent glycogenic effect of GLP-1 (7–36) amide was also reported in rat skeletal muscle from the same laboratory [9], the results were not reproducible [10]. Considering this irreproducibility and previous findings [6, 7], our present findings should indicate that GLP-1 (7–36) amide has no potent effects on glucose metabolism in the liver.

Yours sincerely,

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Fig. 1. The rates of incorporation of D-[U-¹⁴C] glucose into glycogen in isolated rat hepatocytes during a 3 h incubation in the presence of GLP-1 (7–36) amide (○ $n = 11$) or insulin (● $n = 11$) at the concentrations ranging from 10^{-12} to 10^{-7} mol/l. Data are expressed as percentage refer to the control experiment conducted with the incubation of hepatocytes obtained from the same individual rat in the absence of GLP-1 (7–36) amide or insulin. * $p < 0.05$ vs 10^{-12} mol/l insulin

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Diabetes mellitus and Alzheimer's disease

Dear Sir,

Recently in a letter in *Diabetologia* [1] it was suggested that “the occurrence of AGE (advanced glycation end products) in both diabetes and Alzheimer's disease might lead one to predict a higher-than-expected incidence of concurrent diabetes and Alzheimer's disease. However, predictions of diabetes and concurrent Alzheimer's disease unfortunately must await epidemiological analyses . . .” “Conversely, life-long glycation may result in compensations, leading instead to discordance of Alzheimer's disease and diabetes”.

The Umeå Dementia Research Group reported a population-based study of 839 patients with various dementia diagnoses of whom 457 were classified as multi-infarct dementia (MID), 317 as dementia of Alzheimer type (SDAT) and 65 as confusional states [2]. Sixty patients were found to have diabetes, none in the SDAT group, but 55 in the MID group and 5 in the group of confusional states. Oral glucose tolerance tests were performed in patients not known to have diabetes and

compared in patients with SDAT, MID, cerebrovascular diseases, hospitalized control patients and healthy elderly patients. Fasting blood glucose levels were lower and the areas under the oral glucose tolerance curves smaller in the SDAT group compared with the cerebrovascular and the hospitalized control groups. SDAT patients had higher insulin levels than the healthy elderly group. Our findings may be in accordance with the second suggestion mentioned above. However, initially low concentrations of brain transmitters are further negatively influenced by the lack of an important source of energy or perhaps by the lack of a metabolite necessary for the production of transmitters.

Yours sincerely,
F. Lithner

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Elevated circulating adhesion molecules in NIDDM – potential mediators in diabetic macroangiopathy

Dear Sir,

Increased expression of endothelial adhesion molecules (AMs) may have a potential role in accelerated diabetic macroangiopathy [1], possibly stimulated by oxidized low-density lipoproteins (LDL) and free radicals derived from glucose auto-oxidation [2], since “classical” risk factors including hyperlipidaemia, hypertension and obesity do not completely account for the increased incidence of atherosclerosis in diabetes [3]. Such adhesion molecules are involved in chemotaxis of cir-

culating monocytes and binding of leukocytes and platelets to the endothelium. This leukocyte recruitment is considered an initial step in development of atherosclerotic lesions [4]. Raised plasma concentrations of soluble circulating adhesion molecules occurring after proteolytic cleavage of the extracellular domain may indicate endothelial activation and increased interaction of leukocytes and platelets with the endothelium as recently shown for a small number of non-insulin-dependent diabetic (NIDDM) patients ($n = 13$) [5] and diabetic patients not requiring insulin treatment [6].

In a cross-sectional study, we therefore analysed serum concentrations of circulating intercellular adhesion molecule-1 (cICAM-1), vascular cell adhesion molecule-1 (cVCAM-1), and endothelial leukocyte adhesion molecule-1 (cELAM-1 = E-selectin) in a large group of metabolically stable NIDDM patients ($n = 159$) and age-matched healthy subjects ($n = 71$) with no clinically manifest infections and who were not receiving any anti-inflammatory medication. NIDDM patients were treated either by diet alone, with additional sulphonylurea or biguanides ($n = 80$), or by conventional insulin therapy ($n = 79$) with two daily subcutaneous insulin injections (clinical data are given in Table 1).

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