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Letters to the Editor

Direct metabolic effects of gastric inhibitory polypeptide (GIP): dissociation at physiological levels of effects on insulin-stimulated fatty acid and glucose incorporation in rat adipose tissue

Dear Sir,

Drs. Creutzfeldt and Ebert have recently brought up to date the incretin concept [1]. They concluded that gastric inhibitory polypeptide (GIP), also called glucose-dependent insulinotropic polypeptide, is actually the only hormone which fulfils all criteria required for an incretin even if other actually unknown substances exist. On the other hand, they emphasized the direct role of GIP in fat metabolism since fat ingestion is a very potent stimulator of GIP secretion and has no effect on insulin secretion. GIP particularly stimulates the clearance of chylomicron triglycerides from the circulation [2] and activates the lipoprotein lipase in cultured preadipocytes [3]. They concluded that triglyceride uptake would be accelerated by this mechanism. We wish to add some supplementary information on this problem because we have studied another step of lipid metabolism, i.e. the incorporation of fatty acid (FIAT) and glucose (GLIAT) into adipose tissue. We measured the effect of physiological doses of GIP on insulin-stimulated FIAT and GLIAT. Epididymal adipose tissue of Wistar rats was used for this purpose because of its sensitivity to hormonal action and because it well represents what can occur in other adipose tissues. The chosen doses of GIP corresponded to the maximum secretion of GIP observed after glucose ingestion (1 ng/ml), after fat ingestion (2 ng/ml) and finally to a dose slightly greater than the greatest one published in previous studies in pathological cases (4 ng/ml). FIAT and GLIAT were measured according to a method developed in our laboratory [4] and derived from Walldius [5]. Some of the results (FIAT) have been published [6]. They can be summarized as shown in Table 1.

These results indicate that GIP enhanced the insulin-stimulated FIAT in a dose-dependent manner. On the other hand, it has no supplementary effect on GLIAT except for a fair but not significant increase for the highest dose. This might indicate that GIP mainly acts by favoring the passage of FFA through the membrane and that the glucose transport is not dependent on GIP action at physiological levels in normal tissue. It appears that the GIP-induced enhancement of fatty acid entry is not sufficient at these levels for inducing a greater GLIAT than that induced by insulin alone and necessary for triglycerides synthesis. The presence of insulin is necessary for GIP action (6). This still strengthens the relationship existing between GIP and insulin. Moreover, since hyperinsulinism and postprandial hypersecretion of GIP are both present in overweight people as well as in obese animal models, these results are in favor of an important role of GIP in the development of obesity.

Table 1. Effect of GIP on insulin-stimulated (100 μU/ml) FIAT and GLIAT expressed in percent of basal incorporation (without any hormones)

	Dose of GIP (ng/ml)			
	0	1	2	4
FIAT $n=40$	106.4 ± 2.3^{a}	$110.5 \pm 2.1^{a,b}$	$113.0 \pm 3.0^{a,b}$	$118.2 \pm 2{,}7^{a,b}$
GLIAT $n=30$	105.4 ± 1.0^{a}	104.6 ± 1.2^{a}	105.0 ± 2.0^{a}	109.3 ± 1.5^{a}

[a] $p < 0.05$ or less when compared with basal incorporation;
[b] $p < 0.05$ or less when compared with insulin stimulation only

GIP may act by favoring the insulin binding to its receptor on fat cells. Studies of Pedersen and coworkers [7] and of Yki-Järvinen [8] presented in the recent IDF Congress in Madrid that demonstrate an increase of insulin binding of 20–25% 1 h after an oral but not intravenous glucose load or 2 h after the ingestion of a mixed meal, i.e. when GIP levels – in particular – are elevated, are in favor of this hypothesis. However, other factors certainly intervene since glucose transport is also enhanced in both studies.

Finally, the fine regulation of FIAT was achieved by somatostatin [9], which induced a decrease of FIAT at physiological levels. Results from this last study show that the inhibitory action of somatostatin does not act on the mechanism mediated by GIP. Experiments in obese Zucker fa/fa rats are presently under investigation in our laboratory to confirm the role of GIP in obesity.

Yours sincerely,

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