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Preliminary report

The inhibitory effect of proglumide on meal-induced insulin sensitization in rats

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Abstract

We studied the role of cholecystokinin in meal-induced insulin sensitization in rats. Experiments were done with fed or fasted male Wistar rats. Whole-body insulin sensitivity was determined by the rapid insulin sensitivity test in either group. The fed animals were more sensitive to the hypoglycemic effect of insulin than those in the fasted group. Single intravenous doses of proglumide, a cholecystokinin-1 receptor antagonist, decreased insulin sensitivity in fed animals in a dose-dependent manner, whereas it was without effect in the fasted state. We conclude that prandial insulin sensitization strongly depends on pathways regulated by cholecystokinin.

1. Introduction

An endogenous neurogenic insulin sensitization pathway termed the *hepatic insulin sensitization substance* (HISS) mechanism was recently described by Lautt [1]. The essence of this is that eating a meal somehow activates a chain of events involving hepatic nitrergic and cholinergic pathways that results in the release of an undefined substance from the liver termed *HISS* that sensitizes peripheral tissues to the hypoglycemic effect of insulin [2]. It has been shown that both partial hepatic denervation [3] and pharmacologic blockade of either neural nitric oxide synthesis or hepatic muscarinic receptors inhibited postprandial insulin sensitization [2,4]. Because both nitrergic and cholinergic pathways are involved in the effect of cholecystokinin (CCK), a gastrointestinal hormone known to underlie several postprandial adaptive mechanism [5,6], we postulated that the phenomenon of meal-induced insulin sensitization also related to a CCK-regulated processes. This postulation was strongly supported by our accidental finding that the HISS phenomenon was impossible to reproduce in rabbits when anesthesia was achieved by drug combinations containing CCK receptor antagonists such as certain benzodiazepines [7]. We therefore investigated whether CCK was involved in meal-induced insulin sensitization in rats. The experiments presented conform to European Community guiding principles for the care and use of laboratory animals. The experimental protocol applied has been approved by the ethical boards of the University of Debrecen, Hungary (DEMAB 023/2006).

2. Methods

Male Wistar rats (250-350 g) were either fed ad libitum with laboratory chow (fed group) or were fasted overnight (fasted group). The animals were anesthetized with an intraperitoneal injection of thiopental sodium (50 mg/kg). The trachea was cannulated and the animals were allowed to breathe spontaneously. Polyethylene catheters were introduced into the left jugular vein and the carotid artery for insulin and glucose infusion and for blood pressure monitoring as described previously [7]. To determine whole-body insulin sensitivity, we used the rapid insulin sensitivity test (RIST), a method developed by Lautt's [2] group. In brief, after determination of baseline glucose level from arterial samples, 50 mU/kg insulin was infused intravenously over 5 minutes. This was followed by variable rates of 20% glucose infusion. The total amount of glucose (milligrams per kilogram) infused (defined as the RIST index) to maintain baseline blood glucose level characterized whole-body insulin sensitivity [2]. To assess the involvement

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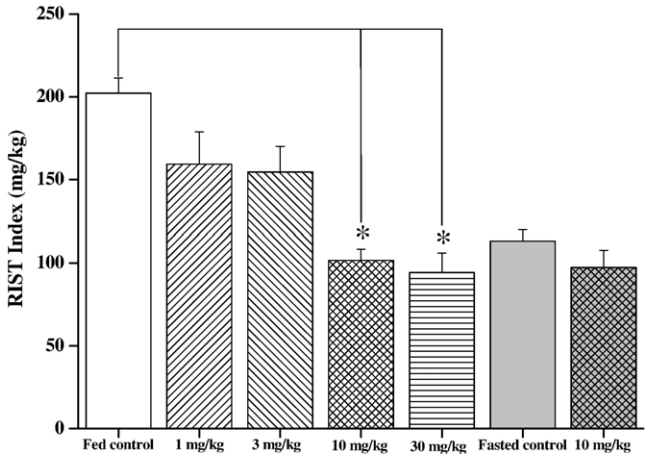

Fig. 1. The results obtained are expressed as means ± SEM obtained with 7 animals per group. The data were analyzed with repeated-measures analysis of variance followed by a modified *t* test according to Bonferroni method for multiple comparisons. The level of significance is at $P < .05$.

of CCK in prandial insulin sensitization, the RIST procedure was accomplished in both fasted and fed animals immediately after the administration of intravenous proglumide (1, 3, 10, and 30 mg/kg; Sigma-Aldrich, Budapest, Hungary), a CCK-1 receptor antagonist and/or its vehicle (isotonic saline).

3. Results

In fed animals, proglumide (1-30 mg/kg) decreased insulin sensitivity as shown in Fig. 1. In animals treated with 10 and 30 mg/kg proglumide, the value of the RIST index was as low as those measured in the fasted animals. The 1 mg/kg dose did not affect insulin sensitivity. In fasted rats, however, the 10 mg/kg dose of proglumide was without effect (Fig. 1).

4. Discussion

That intravenous proglumide, a CCK-1 receptor antagonist, is able to block postprandial whole-body insulin sensitization is the major original finding of the study. The effect is dose-dependent appearing with near maximum value at the 10 mg/kg dose in rats. The results also confirm previous findings that feeding by itself results in an increase in whole-body insulin sensitivity as verified by the RIST method, currently proposed as the most relevant experimental methodology to verify fasting-induced insulin resistance and an increase in insulin sensitivity produced by food intake [2]. Moreover, the proglumide dose exhibiting a near maximum inhibition on food-induced insulin sensitization failed to further promote insulin resistance seen in the fasted state. Therefore, the inhibitory effect of proglumide seems to be rather specific for meal-induced insulin sensitization. Considering that neural nitric oxide synthase inhibition [4], parasympathetic blockade [2], and partial hepatic denervation [3] can block the meal-induced insulin sensitization phenomenon and that the primary site of action for CCK in the gastrointestinal tract is the preganglionic cholinergic-nitrergic neuron [5,8], the present findings strongly suggest that CCK may serve as a trigger for postprandial insulin sensitization first described by Lautt et al as the HISS mechanism. On the other hand, the results call attention to the significance of drugs with CCK receptor blocking property used for whatever indication in provoking metabolic complications.

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