In B. germanica, although the ovaries appear to be capable of vitellogenesis during the last nymphal instar itself[2,7,8], it does not occur until after the adult emergence when the juvenile hormone reappears and acts as a gonadotropin. Last instar nymphs treated in the present study developed, upon metamorphosis, abnormal (hypertrophied and atrophied) ovaries (figures 1–4), presumably due to the simultaneous action of molting hormone and juvenile hormone. For normal vitellogenesis, therefore, the ovaries appear to depend on the presence of juvenile hormone and absence of molting hormone[9,10].

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Effect of vincristine on glucose-induced insulin secretion in man

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Summary. 60 min after the injection of therapeutic doses of vincristine for cancer chemotherapy, there is a reduction of the total (40%) and of the acute phase (43%) areas of insulin secretion induced by a 5-g i.v. glucose load, and the constant of glucose utilization is reduced by 25%. No differences are observed after 3 5-g i.v. glucose loads given at hourly intervals in control subjects.

The participation of the microtubular-microfilamentous system in insulin release has been documented in experimental animals, utilizing isolated pancreatic islets in vitro and rat pancreases in vivo[2–6]. Various agents that influence the system can modify insulin secretion induced by different stimuli[7]. Among these, citochalasin-B[8–11] has a defined action on the microfilaments and colchicine[12–15] interferes with the microtubules; vincristine[10–16] and vinblastine[6–7] disrupt the microtubules and, only partially, the microfilamentous systems.

The aim of this study was to investigate the influence of vincristine (VCR) on insulin release in man, utilizing therapeutic doses for cancer chemotherapy.

Material and methods. 8 patients (4 males and 4 females) suffering from various neoplastic diseases were studied. They required chemotherapy and were at their first treatment. As a control group, 9 patients (5 males and 4 females) without neoplastic diseases were studied. No patient presented a metabolic disease neither were they treated with steroids.

After an overnight fast, each subject was rapidly injected 5 g glucose i.v.[17], 3 times at 1 h by intervals. In the treated group, 1.4 mg/m² of VCR were injected i.v. immediately before the second glucose load. Samples for blood glucose and insulin were drawn from the opposite arm at the following times: 30, 15, 0 min before and 3, 5, 10, 30, 60 min after each load. An additional sample was drawn immediately after VCR in treated patients. Studies were concluded before 13.00. Blood glucose was determined by the glucose-oxidase method and blood insulin by double antibody radioimmunoassay[18].

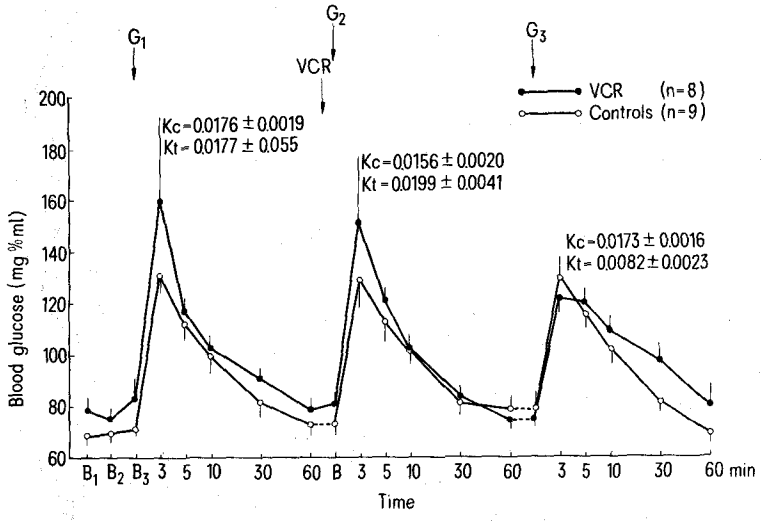

Fig. 1. Glycemias and constants of glucose utilization (K) after 3 5-g i.v. glucose loads (G_1, G_2, G_3). In treated patients 1.4 mg/m² of vincristine (VCR) were injected immediately before the second load. Vertical bars indicate ± SEM. KtG_3 vs KtG_1, $p < 0.05$; KtG_3 vs KcG_3, $p < 0.05$.

The K of glucose utilization was calculated by the formula[19]:

$$K = \frac{\text{Log } C_1 - \text{Log } C_2}{t_2 - t_1} \times 2.3$$

Where: C_1 = blood glucose at 3 min; C_2 = blood glucose at 30 min; t_1 = 3 min; t_2 = 30 min.

The incremental areas of glucose-induced insulin secretion above the mean of basal samples, were calculated differentiating the acute phase area (0–5 min) from the total area (0–30 min). All data have been evaluated according to the analysis of the variance and to Tuckey's test[20].

Results. Blood glucose. A slight but significant ($p < 0.05$) reduction of K is apparent 60 min after VCR. The peaks of glucose concentration are equivalent in treated and control patients (figure 1).

Insulin. There is a reduction of insulin secretion only in the third load of VCR-treated patients; this is apparent as a 26% decrease of the 5 min peak ($p < 0.05$) and as a 40% reduction of the mean total incremental area above the basal levels ($p < 0.05$). The acute phase area showed a reduction of 43% when compared to the same area of the third load of controls ($p < 0.05$) (figure 2).

Discussion. Vincristine interacts with the microtubular-microfilamentous system leading to a loss of its functions[16]. The observed reduction of the total area of insulin secretion suggests that, also in the human pancreatic beta cell, the microtubular system could play a role in insulin release. The partial inhibition of the acute phase that follows the third glucose load in treated group might suggest that also the microfilamentous system could be involved in insulin release. This phenomenon could be ascribed to the known VCR-induced partial disruptions of microfilaments[15], that are considered to be important among the mechanisms of emiocytosis[5]. This hypothesis is in keeping with what was previously shown by Van Obberghen et al.[9] and by Orci et al.[4] in their studies concerning the effect of citochalasin-B, and by Lacy et al.[8]. These latter authors studied the effect induced on insulin release in the rat B-cells by citochalasin-B after treatment with vinblastine. 2 other remarks may be done: first, that human pancreas is able to respond to as little as 2.1×10^{-6} moles of VCR, administered as a bolus, while other authors found a reduction of insulin secretion using higher concentrations of the drug (between 2.5×10^{-3} and 2.5×10^{-5} moles) by continuous infusion in isolated rat pancreas[4–13]. As found in animals[3–16], human pancreas requires at least 60 min before the biological effect of VCR is observed. Secondly, that 5 g glucose load is a good insulinogenic stimulus, that can be repeated at one hourly intervals at least 3 times. In fact, no significant difference was observed in the patterns of blood glucose, K values, insulinemias and areas of insulin secretion in the control subjects.

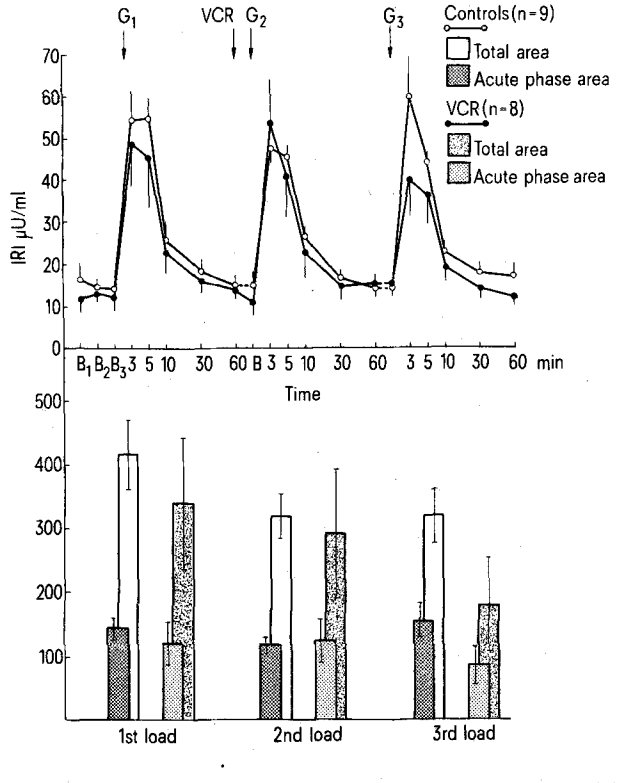

Fig. 2. Insulinemias and areas of acute (0–5 min) and total (0–30 min) phases of insulin secretion after 3 5-g i.v. glucose loads (G_1, G_2, G_3). In treated patients, 1.4 mg/m² of vincristine (VCR) were injected immediately before the second load. Vertical bars indicate ± SEM. IRI values: 5 min G_3 vs 5 min G_1 – VCR, $p < 0.05$. IRI areas: a) acute phase: VCR vs controls – 3rd load, $p < 0.05$; b) total phase: 3rd load vs 1st load – VCR, $p < 0.05$.

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