Inhibition by Ether of Glucose-stimulated Insulin Secretion in Isolated Pieces of Rat Pancreas

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Addition of glucose (16.7 mM) to isolated pieces of rat pancreas increased insulin secretion 5.4-fold over basal secretion rates. Ether at 1, 1.5 and 2 MAC inhibited this insulinogenic effect of glucose in a dose-related manner by 5, 18 (P < 0.01) and 29 (P < 0.01) per cent, respectively. (Key words: Anesthetics, volatile; diethyl ether. Hormones: insulin. Pancreas.)

Altersations in carbohydrate metabolism are commonly observed during inhalational anesthesia in vivo.1,2 Whether the observed changes are due to direct or indirect actions of these anesthetics has not been determined. Merin et al. demonstrated an inhibition of glucose-induced insulin release in human subjects during halothane and methoxyfuran anesthestia.3 A similar result was seen by Aynsley-Green et al., with halothane in fed rats.4 We have shown that in the case of halothane, this inhibition observed in vivo is due in part to a direct inhibitory effect of halothane on the pancreas, since the inhibition can be observed in isolated pieces of rat pancreas.5

Yoshimura et al. found diethyl ether anesthesia caused an increase in blood glucose with a concomitant increase in plasma insulin.6 Since plasma catecholamines are known to be increased during ether anesthesia, many of the actions of ether on carbohydrate metabolism have been attributed to the indirect effects of catecholamines on hepatic glycogenolysis. In rats presumably depleted of hepatic glycogen by starvation for 48 hours, however, ether still increased blood glucose before and after a glucose load.7 This effect was attributed to an interference by ether with peripheral glucose utilization rather than to decreased pancreatic responsiveness.

Since the direct effect of ether on insulin release has not been studied, we proposed to determine whether ether has a direct depressant effect on glucose-stimulated insulin release in isolated pieces of rat pancreas.

Methods

Pancreatic tissue was quickly removed from fed Sprague-Dawley rats (200–300 g) and placed into a petri dish containing cold (0 C) glucose-free bicarbonate-buffered incubation medium.7 Extrainuous adipose tissue and lymph nodes were trimmed away, and the glandular portion was cut with single-edged razor blades into small pieces (2–4 mg) and rinsed twice with cold buffer. Four pieces were randomly chosen and carefully transferred to small ground-glass-stoppered Erlenmeyer flasks (10 ml) containing cold bicarbonate-buffered incubation medium (2.0 ml), which consisted of glucose (0–300 mg/100 ml), bovine serum albumin (1 per cent, w/v; bovine albumin, fraction V), and guinea pig anti-insulin serum (GPAIS, our lot 524). The albumin was not dialyzed prior to use. Each flask was equilibrated against oxygen (95 per cent) and carbon dioxide (5 per cent) and incubated for 90 min at 37 C. At the end of the incubation period the pancreatic pieces were gently blotted and weighed.

Immediately prior to incubation, sufficient ether was added by a microliter syringe below the surface of the medium to the appropriate flasks to achieve concentrations of 9.95, 14.93 and 19.90 mM in the incubation medium and equilibrium partial pressures corresponding to 1, 1.5 and 2 MAC in the gas phase above the medium. The medium–gas partition coefficient necessary for the preceding step was assumed to be the same as the corresponding water–gas value of 13.1 obtained by Eger et al.8 This value was obtained at low partial pressures of ether in the range used in the present study. The presence of the small amounts of albumin and salts in our medium would not be expected to alter the partition coefficient more than a few per cent, if at all, since the blood–gas partition coefficient determined by the above-mentioned investigators was 12.1.

In order to calculate the total amount of ether to be added to each flask, we: 1) calculated the amount of ether in each ml of saline solution necessary to achieve the desired concentration; 2) divided this amount by the saline solution–gas partition coefficient for ether; 3) multiplied the amount found in step 1 by the number of ml of saline solution in the flask;

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4) multiplied the amount found in step 2 by the number of ml of air in the flask; 5) added the amounts found in steps 3 and 4.

Details of the method used to measure insulin secretion in vitro were reported previously. GPAIS was added to the medium to protect secreted insulin against lytic substances released from acinar tissue and to provide an easy means of measuring secreted hormone. Briefly, sufficient GPAIS was added to the incubation medium to bind about twice the insulin that the incubated pieces were expected to secrete. At the end of the incubation period, samples (0.2 ml) of medium were taken and the unneutralized antiserum measured by radioimmunoassay. Insulin secreted into the medium could be calculated from the observed decrease in reactive antibody content during incubation.

Insulin secretion in the presence of ether and insulin secretion in its absence were compared by the Student t test.

Results

Insulin secretion by pieces of rat pancreas was increased from a basal value of 38.1 ± 4.5 µU/mg/90 min in the absence of glucose to a stimulated level of 205.9 ± 6.1 µU/mg/90 min when glucose (300 mg/100 ml) was added to the medium. Ether progressively decreased this glucose-induced secretion in a dose-dependent manner (table 1).

Discussion

The present studies indicate that ether, like halothane, significantly depresses insulin secretion by a direct action on the pancreas at concentrations in the clinical range (1.5–2 MAC). In spite of the direct depressant action of ether on insulin secretion, plasma levels of insulin are increased in patients anesthetized with ether. This increase in plasma insulin is probably associated with the demonstrated hyperglycemic action of ether. It is likely, then, that the increased levels of insulin during ether anesthesia are less than would be expected in response to the hyperglycemia alone.

Although there is no other report, to our knowledge, concerning the effect of ether on isolated pancreas preparations, another report dealing with the effect of halothane on insulin release has appeared. This report states that halothane had no significant effect on glucose-stimulated insulin secretion in the isolated perfused rat pancreas. There are a number of criticisms one might make regarding the analysis and interpretation of the data: 1) the number of experiments performed was insufficient—four test experiments with halothane, two control; 2) there was no statistical evaluation of the data; 3) although the insulinogetic responses to glucose infusion were similar in the four test experiments exposed to halothane, compared with the two unanesthetized controls, the test group showed a much greater insulin response to a 100-ml pulse of glucose prior to exposure to halothane (721 vs. 469 per cent) and a much greater insulin response to glucose infusion following termination of halothane administration (369 vs. 199 per cent). Rather than indicating a lack of halothane effect, the data suggest a marked inhibitory effect of halothane on insulin secretion.

Insulin is not the only endocrine hormone whose release is inhibited by halothane and ether. Acetylcholine-induced liberation of catecholamines from isolated perfused bovine adrenals is inhibited 50 per cent by 25.7 mm diethyl ether and 0.25 mm halothane.

References

1. Greene NM: Inhalation Anesthetics and Carbohydrate Metabolism, Baltimore, Williams and Wilkins, 1963
2. Greene NM: Insulin and anesthesia, ANESTHESIOLOGY 41:75–79, 1974