Medical Intelligence

Insulin and Anesthesia

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In-vitro evidence based upon plasma insulin and glucose levels and insulin:glucose ratios suggests that certain anesthetics may partially inhibit insulin release from the pancreas, but considerable individual variation in the actions of the various anesthetics appears likely. More reliable in-vitro data indicate that halothane decreases insulin release in response to hyperglycemia, but the in-vitro effects of other anesthetics have not been reported. Similarly, while in-vitro experiments suggest that certain anesthetics may inhibit metabolic activity of circulating insulin, in-vitro data indicate that diethyl ether, the only agent reported to date, has no effect on insulin-mediated glucose uptake, even though it affects other metabolic responses to insulin. (Key words: Hormones; insulin; Metabolism: carbohydrate.)

The effects of anesthetics on carbohydrate metabolism are often considered without reference to the possibility that anesthetics may affect either metabolic activity of insulin or the rate at which insulin is released from the pancreas. The following review considers what is, and what is not, known about insulin activity and release during anesthesia and surgery. As will become apparent, what is unknown exceeds by several orders of magnitude what is known in this complex field.

Plasma Insulin Levels

One means of evaluating anesthetic effect on insulin relies upon measurement of blood levels of insulin during anesthesia. In the only report on the effect of diethyl ether anesthesia on blood levels of insulin, plasma insulin levels were found to be increased in normal man from a control value of 16 μU/ml to 30 μU/ml after 90 minutes of

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anesthesia. The increase in plasma insulin levels during diethyl ether anesthesia stands in contrast to results reported with other anesthetics. In the absence of surgery, anesthesia in normal man is unaccompanied by significant change in plasma insulin level during halothane,1-3 methoxyflurane,2,4 thioental–nitrous oxide,2 enfurane,2 cyclopropane,7 or spinal anesthesia. There are no data on plasma insulin levels during other forms of general anesthesia or other types of regional anesthesia.

Insulin:Glucose Ratios

Plasma insulin levels by themselves are of limited value. They reflect the rate at which insulin enters the blood stream and the rate at which it is removed from blood (utilization). Plasma levels give no information on the rate at which insulin is released from the pancreas. Furthermore, they fail to indicate what effects, if any, anesthetics may have on the ability of insulin to effect transport of glucose across cell membranes. Because blood glucose levels normally regulate insulin release, the ratio between plasma insulin and blood glucose levels has been suggested to provide more useful information than insulin levels alone. The theory is that since hyperglycemia normally produces elevation of plasma insulin, and hypoglycemia leads to decreased release of insulin, therefore an increase in the normal insulin:glucose ratio indirectly indicates increased release, while a decrease in the ratio represents inhibition of release. Studies have been made of the effects of anesthesia on the ratio between plasma insulin and blood glucose. Yoshimura and associates1 found that, while halothane anesthesia in man was unaccompanied by changes in plasma insulin,
blood glucose levels rose slightly but significantly. Merin et al.\textsuperscript{2} found essentially the same thing, not only with halothane but also with methoxyflurane: while blood glucose levels rose with both agents, there was either no elevation of plasma insulin (methoxyflurane) or a proportionately smaller elevation (halothane). Similar findings during cyclopropane anesthesia have been reported.\textsuperscript{7} Although blood glucose levels rose significantly from 82 ± 2 to 119 ± 7 mg/100 ml after 45 minutes of cyclopropane anesthesia in normal man, plasma insulin levels decreased from 11.8 ± 1.5 to 9.9 ± 1.0 }\mu{}\text{U/ml. With halothane, methoxyflurane and cyclopropane, therefore, the ratio of plasma insulin to blood glucose decreased during anesthesia. It decreased either because insulin levels fell at a time when glucose levels rose, or because insulin levels increased less than glucose.

However, not all general anesthetics decrease the ratio between insulin and glucose. Neither insulin nor glucose level changed significantly during 40 minutes of enflurane anesthesia in normal man,\textsuperscript{6} the ratio between the two therefore remaining unchanged. Diethyl ether, on the other hand, increases the insulin:glucose ratio. After 90 minutes of diethyl ether anesthesia without surgery in normal man, blood glucose levels were found to increase from 83 to 113 mg/100 ml at a time when plasma insulin levels rose even more, from 16 to 30 }\mu{}\text{U/ml, the ratio between the two therefore increasing from .192 to .265.

Thiopental–nitrous oxide anesthesia has been reported to be associated with a decreased insulin:glucose ratio. Plasma insulin values were unchanged at a time when blood glucose levels rose. Patients were studied, however, only prior to anesthesia and during anesthesia when “surface” surgery was being performed. The possible effect of surgical stimulation on insulin:glucose ratios cannot, therefore, be dissociated from the possible effects of thiopental–nitrous oxide anesthesia.

The effect of surgery per se on the ratio between insulin and glucose is not clear. The ratio does not change during surgery performed with spinal anesthesia,\textsuperscript{5} but since the operative site is denervated by spinal anesthesia afferent stimuli would not be expected to affect hormonal balance. During enflurane anesthesia, surgical stimulation appears to have no significant effect on insulin:glucose ratios (table 1). With cyclopropane, the insulin:glucose ratio associated with 45 minutes of anesthesia without surgery, .144 before induction and .083 during anesthesia, decreased slightly further to .071 after one hour of surgery plus anesthesia. This further decline, of doubtful statistical significance, could have been caused by operative stimuli. It could also represent a further modest decrease in insulin:glucose ratio due to the fact that cyclopropane, which decreased the ratio in the preceding 45 minutes, had been administered for an additional 60 minutes.

**Sympathetic Effects on Insulin Release**

A decrease in the ratio of plasma insulin to blood glucose could result from inhibition of insulin release from the pancreas. Sympathetic stimulation inhibits insulin release.\textsuperscript{10} The decreased insulin:glucose ratio during cyclopropane anesthesia might, therefore, be hypothesized as being the result of the well-recognized increase in sympathetic tone produced by this anesthetic. Such a sympathetically mediated inhibition of insulin release might, for example, explain in part the decreased glucose consumption observed during the hyperglycemia of cyclopropane anesthesia.\textsuperscript{11} However, diethyl ether, an agent which also increases sympathetic activity, is associated with elevation, not depression, of plasma insulin levels. Furthermore, although surgical stimuli increase activity of the sympathetic nervous system during general anesthesia, especially during light levels of anesthesia, the onset of surgery has been shown to be accompanied by unpredictable changes in plasma insulin and plasma insulin:glucose ratios. “Surface” surgery during light thiopental–nitrous oxide anesthesia in man is, for example, unaccompanied by changes in plasma insulin levels,\textsuperscript{9} and 60 minutes after the start of surgery plasma levels of insulin do not differ significantly from the levels observed before surgery during halothane, \textsuperscript{3} enflurane,\textsuperscript{6} or cyclopropane\textsuperscript{5} anesthesia, despite the fact that onset of surgery...
is accompanied by other evidences of sympathetic stimulation.

**Other In-vivo Studies**

Although plasma insulin:glucose ratios have enjoyed a vogue in recent years, the consensus today is that they are of very limited value. They may indicate in a general way that something has changed, but insulin:glucose ratios are inadequate to differentiate among various possible causes of altered glucose metabolism which may be associated with changes in the ratio. Under the special circumstances represented by the state of anesthesia, the utility of plasma insulin:glucose ratios is particularly limited by the fact that they are based on the assumption that the metabolic activity of insulin in effecting transport of glucose across cell membranes is unimpaired by the anesthetic itself. A decrease in the plasma insulin:glucose ratio could indeed indicate insulin release from the pancreas had been inhibited, with hyperglycemia resulting from inadequate amounts of insulin in the circulating blood. A decrease in the ratio could also, however, indicate that during anesthesia the insulin released is no longer capable of serving its normal metabolic role, in which case hyperglycemia would also result, with a decrease in the insulin:glucose ratio.

Because of the limitations inherent in interpreting plasma insulin:glucose ratios, attempts have been made to determine in vivo the effects of anesthetics on insulin by other techniques. These have included: 1) measuring the response of blood glucose levels when exogenous insulin is administered; 2) measuring blood glucose levels when glucose and insulin are simultaneously administered; 3) measuring plasma insulin levels when exogenous glucose is administered.

These studies have indicated that diethyl ether inhibits insulin activity in man and that halothane anesthesia and surgery inhibit insulin release. In-vivo studies such as these may present certain advantages over reliance upon plasma insulin:glucose ratios, but they, too, have major limitations, especially when performed in man under clinical conditions. Chief among these limitations is the fact that they must be performed under such pharmacological and biochemically unsteady states that their interpretation in meaningful metabolic terms becomes difficult, if not impossible. The in-vivo situation is too complex, with too many things simultaneously happening, to allow accurate definition of metabolic activity of insulin and the rate at which it is released from the pancreas.

**In-vitro Studies**

The effects of anesthetics on insulin release and insulin activity can be proven only in vitro, under conditions which allow adequate control of all the various direct and indirect factors which otherwise might distort the results. The only in-vitro study on the effects of an anesthetic on insulin release showed that halothane inhibited in a concentration-dependent manner the increase in release of insulin from isolated pieces of rat pancreas normally produced by hyperglycemia. Halothane had, however, no effect on non-glucose-mediated insulin release. One might anticipate, therefore, that halothane might have little effect on basal levels of insulin release in vivo.

The only study of the effect of an anesthetic on insulin activity in vitro is that of Brunner. Using the isolated rat hemidiaphragm as a model, Brunner found that in concentrations compatible with those producing surgical levels of anesthesia, diethyl

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**Table 1. Effect of Surgical Stimulation on Insulin:Glucose Ratio in Man**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Anesthesia (45 Min)</th>
<th>Operation (60 Min)</th>
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<tbody>
<tr>
<td></td>
<td>Gl</td>
<td>Ratio</td>
<td>I</td>
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<tr>
<td>Etomidate</td>
<td>13.2 ± 1.6</td>
<td>0.037</td>
<td>12.1 ± 1.5</td>
</tr>
<tr>
<td>Cyclopropane</td>
<td>11.5 ± 1.5</td>
<td>0.02</td>
<td>9.9 ± 1.0</td>
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* Plasma insulin: μU/ml; mean ± SE.
1 Blood glucose: mg/100 ml; mean ± SE.
ether significantly decreased glucose uptake by resting muscle. It did so in the absence of insulin, and it did so in the presence of insulin (table 2). Diethyl ether decreased glucose uptake by approximately 3.0 μM/g/hour, regardless of whether insulin was present. Similarly, the increase in glucose uptake produced by insulin in the absence of diethyl ether, 11.5 μM glucose/g/hour (from 21.9 to 33.4), was essentially the same as the increase in glucose uptake which resulted when insulin was present during exposure to diethyl ether, 12.5 μM glucose/g/hour (from 17.9 to 30.4). Diethyl ether, therefore, does not change the normal effect of insulin on glucose uptake in resting skeletal muscle, and ether-induced inhibition of glucose uptake by resting skeletal muscle does not represent an anti-insulin effect.

Diethyl ether did, however, have other effects on metabolic responses to insulin, including the effect of insulin on lactate production (table 3). In the absence of diethyl ether, insulin had no effect on the rate at which lactate was produced by resting muscle. In the presence of diethyl ether, however, insulin significantly increased lactate production, and furthermore, it increased the lactate production associated with diethyl ether alone. The non-effect of insulin on lactate formation without anesthesia was replaced by a 6.7 μM/g/hour increase when diethyl ether was present. Or, from a different point of view, the 5.1 μM/g/hour increase in lactate production induced by diethyl ether in the absence of insulin (from 11.2 to 16.3 μM/g/hour) was greatly exceeded by the corresponding value in the presence of insulin (from 11.5 to 23.0 μM/g/hour, an increase of 11.5 μM/g/hour).

Diethyl ether was also shown by Brunner to alter the effect of insulin on glycogen formation. In the rat hemidiaphragm, insulin increased glucose uptake by 11.5 μM/g/hour in the absence of anesthetic, and 8.1 μM or 70 per cent of the increased glucose uptake was converted to glycogen. In the presence of diethyl ether, insulin still increased glucose uptake (by 12.5 μM/g/hour), but only 6.3 μM, or approximately 50 per cent, of the increased uptake was converted to glycogen.

Brunner's data indicate that while diethyl ether does not alter insulin activity in terms of glucose uptake, it does alter disposition of glucose after it has been taken up by the cell. It does this either by inhibiting insulin activation of glycogenolysis or by increasing glycolysis. Inhibition of the rate at which intracellular glucose substrates are converted to glycogen would result in routing of proportionately more of the substrates through glycolytic pathways, with consequent increase in lactate production. On the other hand, preferential stimulation of glycolysis without inhibition of glycogenolysis would produce much the same picture.

Brunner's data emphasize that the hyperglycemia associated with diethyl ether cannot be ascribed to inhibition of insulin-induced uptake of glucose. Hyperglycemia might, however, be contributed to by an anesthetically induced depression of glucose transport across cell membranes.18

Merin19 has shown (1970) that insulin is capable of increasing myocardial function in the halothane-depressed heart. This suggests that the negative inotropic of halothane may be related in part to its effect on glucose uptake. Merin's study did not determine, nor was it designed to determine, whether the effect of insulin on glucose uptake by the heart and the effect of insulin on myocardial function were altered by halothane.
References

18. Greene NM: Inhalation anaesthesit and permeability of human erythrocytes to monosaccharides. ANESTHESIOLOGY 26:731–742, 1955

Trauma

EMERGENCY MEDICAL CARE The Illinois Trauma Program, implemented in July 1971, has established 21 local, eight area-wide, and eleven regional centers. Each center is staffed by a Trauma Coordinator, a veteran medical trained health professional employed by the Illinois Division of Emergency Medical Services and Highway Safety. These coordinators work to improve liaison between hospital chiefs of staff, law enforcement officers, and ambulance rescue organizations. They provide training programs for the latter and collect data for a computerized Trauma Registry. The Trauma Program has succeeded in directing the flow of the injured to Trauma Centers. (Boyd, D.R., Mains, K.D., and Flashner, B.A.: A Systems Approach to Statewide Emergency Medical Care. J Trauma 13: 276, 1973.)