SOME EFFECTS OF ANAESTHESIA AND SURGERY ON CARBOHYDRATE AND FAT METABOLISM

BY
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SUMMARY

The effects of emotional stress, nitrous oxide and halothane anaesthesia, a 1-minute period of hypoxia, and surgery, on the blood sugar, plasma free fatty acids (FFA) and insulin were investigated. The emotional stress of being brought to the operating theatre and the stress of surgery seem to be more important than anaesthesia in causing a rise in blood sugar and plasma FFA. There was a corresponding fall in levels of plasma insulin. The infusion of phentolamine in two patients did not prevent the failure of insulin response to injected glucose during surgery. The clinical significance of this temporary state of glucose intolerance is discussed.

In a preliminary communication (Allison, Prowse and Chamberlain, 1967), a failure of insulin response to injected glucose during surgery and in the acute phase of myocardial infarction was reported. More recently (Allison, Hinton and Chamberlain, 1968) a similar phenomenon has been demonstrated in burned patients. It was suggested that this effect was a non-specific response to stress, mediated by increased adrenaline secretion and sympathetic activity, in view of the observation by Porte and associates (1966) that insulin response to injected glucose could be suppressed by adrenaline infusion. Porte and associates showed also that suppression by adrenaline of the insulin response to glucose could be prevented by alpha but not by beta adrenergic blockade. The present study was designed to examine the effects of the emotional stress of impending operation, nitrous oxide anaesthesia, hypoxia and surgery on the levels of blood sugar, plasma free fatty acids and immunoreactive insulin (i.r.i.). We also wished to examine further, the failure of insulin response to glucose during surgery and to test the effect upon this of infusing phentolamine, an alpha adrenergic blocker.

GROUP 1

In 7 patients, a standard 25-g intravenous glucose tolerance test (GTT) (Samols and Marks, 1965) was performed twice; the first test was on the day before the operation, at the same time of day as the operation was expected to take place with the patient under the same fasting conditions. On the day of operation, blood samples were taken in theatre before induction of anaesthesia and 20 minutes after induction, the operation having started. A second i.v. GTT was then performed. No premedication was given in 5 of these patients. Papaveretum and hyoscine was given in one case and pethidine and atropine in another. Anaesthesia was induced with thiopentone (250-350 mg) or methohexitone (70–90 mg) and maintained with nitrous oxide, oxygen and tubocurarine. In 5 patients 2 per cent halothane was used during part of the operation.

GROUP 2

In 2 patients the same protocol was adopted as in group 1, except that, during the operation phentolamine was infused in 0.9 per cent saline at a rate of 120–150 mg per hour to maintain a systolic arterial pressure of 80–95 mm Hg.

PATIENTS

Thirteen patients (age range 23–67 years) undergoing a variety of surgical procedures, ranging in severity from exploration of the common bile duct to stripping of varicose veins, were studied. The patients were divided into three groups.

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Blood sugar, plasma insulin and FFA were studied in 4 patients without injection of glucose. Blood samples were taken in the ward, 20 and 10 minutes before the patient was brought to the operating theatre. Further samples were taken 5 and 10 minutes after reaching the theatre and then 10 and 20 minutes after induction of anaesthesia and before the operation had started. The patients were then subjected to 1 minute breathing 5 per cent oxygen, which was sufficient in each case to lower the arterial Po2 to between 40 and 50 mm Hg as measured with a Po2 electrode. Samples were taken 1 and 10 minutes following the end of this period of relative hypoxaemia. Finally, blood samples were taken 10 and 20 minutes after beginning the operation. Anaesthetic technique was the same as in group 1 except that in none of the patients was premedication or halothane used.

METHODS

Glucose tolerance tests.

All blood samples were withdrawn from an antecubital vein. A sample was taken for basal levels of blood sugar, plasma FFA and insulin. Glucose 25 g in 50 g/100 ml solution was then injected over 3 minutes into a forearm vein. Blood samples were taken at 2, 5, 10, 20, 30, 40, 50 and 60 minutes after the end of the injection. Pre-operative and operative glucose tolerance tests were compared as follows: (a) in terms of the K value or slope of the logarithmic plot of the glucose curve from 20 to 60 minutes (Samols and Marks, 1965); (b) for insulin response to the injected glucose; and (c) for changes in levels of plasma FFAs.

Blood sugar.

This was measured in duplicate as total reducing substances by the Neocuprin autoanalyzer technique. This is a colorimetric technique involving reduction of a copper salt. Samples were taken into fluoride tubes and estimated on the same day or stored at 4°C until the following day. The reproducibility of this analytical technique is within 2 per cent.

Plasma insulin.

This was measured in triplicate by a modification of the method of Hales and Handle (1963). Samples were taken into sodium heparin tubes and placed in the refrigerator at 4°C pending plasma separation. The plasma was then separated within 2 hours and stored at −20°C until it could be assayed. Samples from both glucose tolerance tests from the same patients were estimated in the same assay. The accuracy of the technique may be gauged by the fact that assays of insulin levels from specimens of pooled plasma measured over a period of 3 months gave a coefficient of variation of 8.5 per cent.

Plasma-free fatty acids.

Blood samples were treated in the same way as for insulin. Plasma was stored at −20°C for a maximum of 24 hours and free fatty acids were then extracted by the method of Dole and Meinertz (1960) and estimated colorimetrically in duplicate by the method of Duncombe (1963). The reproducibility of paired samples was within 5 per cent.

RESULTS

Group 1.

Basal values. The blood sugar rose from a mean level of 86.3 mg/100 ml to a mean level of 94.3 mg/100 ml 20 minutes after induction. The difference is significant (P<0.01). The operation had started by the time the second sample was taken, so that it was not possible to distinguish between the effect of anaesthesia and surgery on the blood sugar. It was observed that the level of blood sugar in theatre even before anaesthesia was higher than that found on the ward the previous day in the same patient.

Glucose tolerance tests. Mean values and ranges of blood sugar, plasma insulin and FFA are shown in figures 1A (pre-operative) and 1B (operative), K values being normal, i.e. >1.0 (Samols and Marks, 1965), in all pre-operative tests. In every case the K value was lower for the test performed during operation. In all patients the insulin response to glucose was lower during surgery than pre-operatively. The degree of suppression of insulin response was greater in more severe operations involving laparotomy than in a simple herniorrhaphy or varicose veins operation. For example, a patient of 49 years undergoing exploration of the common bile duct had a pre-operative K value of 2.04 which fell during operation to less...
than 0.1, whereas a similar patient having a stripping of varicose veins had a pre-operative control K value of 3.9 which fell only to 2.0 during operation. The first patient had no insulin response at all during operation whereas the second one had some insulin response to the added glucose, albeit less than in the control study. The later rise in insulin levels seen in figure 1B is due to the fact that in some patients the operation was being completed before the end of the test. The end of the operation is a time when we have previously noticed a rise in insulin levels (Allison, Prowse and Chamberlain, 1967). Plasma FFA levels were higher and the fall in FFA levels less after injection of glucose during surgery as compared with the pre-operative study.

**Group 2.**

Phentolamine in the 2 patients studied had no apparent effect in preventing suppression of insulin response to glucose. The results from one of the two patients in this group are shown in figure 2. Qualitatively they are indistinguishable from those found in group 1.

**Group 3.**

The results are shown in table I. Although there is a small rise in blood sugar and FFA following anaesthesia and following the 1-minute period of hypoxia, this is not statistically significant (P>0.05). There is, however, a significant rise (P<0.05) in both these values associated with moving the patient from the ward to the anaesthetic room and with surgery. The fall in plasma insulin is significant overall (P<0.01) but not between each step. There was no statistically significant difference between the members of each pair of values for sugar or FFA within each step and because the time interval between each step was so small (mean 10 minutes); this suggests
that the changes in levels of these metabolites were stepwise rather than continuous throughout the period of study.

**DISCUSSION**

There are reports of a rise in blood sugar associated with most anaesthetics. In 1853 Reynoso reported glycosuria associated with ether anaesthesia. Drucker and colleagues (1959) demonstrated glucose but not fructose intolerance under ether anaesthesia. In a recent review, Greene (1968) discussed the effect of halothane and pointed out how anaesthetic management may affect the rise in blood sugar; for example, thiopentone may diminish the hyperglycaemic effects of inhalation anaesthetics. For this reason, it is difficult to assess the effect of nitrous oxide on blood sugar, for it is seldom used alone. With the form of anaesthetic management used in this study, it is clear that the emotional stress of being moved to the operating theatre and the stress of operation were more important factors than was anaesthesia in raising the blood levels of sugar and FFA. The level and length of the hypoxaemia used here was without significant effect on the blood levels of these metabolites, suggesting that the very short episodes of hypoxia sometimes experienced during anaesthesia play no part in the changes described here. Greene (1968) casts doubt on the role of the sympathetic nervous system in the hyperglycaemia associated with inhalation anaesthetics, particularly halothane, and has pointed out that halothane depresses sympathetic nervous activity. Whatever the truth of this argument, it is apparent from the present study that

**FIG. 2**

Glucose tolerance tests before (○⋯⋯○) and during (×⋯⋯×) operation. Phentolamine 130 mg/hr infused during operation.

**TABLE I**

*Mean values (±1 SD) in 4 subjects to show changes in sugar, FFA and insulin levels in the blood.*

For explanation of column 2 (Time (min)) see text under Patients (Group 3).

<table>
<thead>
<tr>
<th>Steps</th>
<th>Time (min)</th>
<th>Sugar (mg/100)</th>
<th>FFA (µ equiv/l.)</th>
<th>Insulin (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>On ward before theatre</td>
<td>20</td>
<td>84.8±8.1</td>
<td>667±246</td>
<td>18.3±4.6</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>84.3±6.7</td>
<td>656±278</td>
<td>18.0±5.7</td>
</tr>
<tr>
<td>After taking to theatre</td>
<td>5</td>
<td>90.0±4.4</td>
<td>855±216</td>
<td>19.5±6.7</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>89.5±5.3</td>
<td>948±237</td>
<td>16.0±4.5</td>
</tr>
<tr>
<td>After induction of anaesthetic</td>
<td>10</td>
<td>92.0±4.9</td>
<td>962±279</td>
<td>14.3±2.6</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>94.3±9.8</td>
<td>1074±217</td>
<td>14.0±3.7</td>
</tr>
<tr>
<td>After 1 minute hypoxia</td>
<td>1</td>
<td>98.8±13.6</td>
<td>1109±264</td>
<td>13.0±2.9</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>97.0±12.9</td>
<td>1066±205</td>
<td>11.5±3.0</td>
</tr>
<tr>
<td>After operation begun</td>
<td>10</td>
<td>107.5±23.2</td>
<td>1281±214</td>
<td>11.3±5.3</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>114.8±18.2</td>
<td>1448±298</td>
<td>11.8±6.2</td>
</tr>
</tbody>
</table>
neither thiopentone, nitrous oxide nor halothane was able to prevent the rise in blood sugar and FFA associated with surgery. Neither did they, or the drugs used for premedication, prevent the glucose intolerance and suppression of insulin response to glucose, associated with operation. The changes in blood sugar and FFA could be explained on the basis of increased sympathetic activity causing increased lypolysis and glyco-
genolysis, but it is apparent that the concomitant suppression of insulin secretion must also affect these values. Porte and associates (1966) demonstrated that the suppression of insulin response to glucose caused by adrenaline could be prevented by phentolamine. In this study the suppression of insulin response induced by surgery was not prevented by phentolamine. It is possible, therefore, that we are dealing with a different mechanism from that described by Porte and associates, but Havel (1968) has pointed out that it is much more difficult to block the effects of endogenously produced catecholamines than those of artificially infused ones. It is possible, therefore, that in this study phentolamine was an insufficiently powerful blocker to prevent insulin suppression. It seemed unjustifiable to use the more powerful drug, phenoxybenzamine, acutely in these patients, in view of its prolonged action and the dangers associated with it. The mechanism of insulin suppression in these patients still remains a matter for speculation, although the rise in insulin level seen at the end of operation in this study and in a previous study (Allison, Prowse and Chamberlain, 1967) seems to suggest that adrena-
line mechanism is likely.

The clinical significance of this phenomenon rests on the fact that stress causes a temporary diabetic state. Behaviour in response to infused glucose is different from normal in this situation, causing hyperglycaemia and, by its osmotic effects, expansion of the extra-cellular space and osmotic diuresis. Suppression of insulin secretion also explains partly why mild or latent diabetics show a worsening of the diabetic state as a result of stress. Increased secretion of insulin antagonists, such as growth hormone and cortisol, must also play some part. As described previously (Allison, Prowse and Chamberlain, 1967), in patients on cardiopulmonary bypass in whom large amounts of glucose may be used in the pump priming, the rise in insulin secretion which occurs at the end of operation causes a fall in serum potassium and an increased tendency to digitalis induced arrhythmias.

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REFERENCES


bolism during ether anesthesia. 1: Effect of ether on glucose and fructose metabolism. Metabolism, 8, 827.

Duncombe, W. G. (1963). The colorimetric micro-


