Effect of Halothane Anesthesia on Glucose Utilization and Production in Adolescents

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Background: It should be possible to avoid variations in plasma glucose concentration during anesthesia by adjusting glucose infusion rate to whole-body glucose uptake. To study this hypothesis, we measured glucose utilization and production, before and during halothane anesthesia.

Methods: After an overnight fast, six adolescents between 12 and 17 yr of age were infused with tracer doses of [6,6-2H2]glucose for 2 h before undergoing anesthesia, and the infusion was continued after induction, until the beginning of surgery. Plasma glucose concentration was monitored throughout, and free fatty acids, lactate, insulin, and glucagon concentrations were measured before and during anesthesia.

Results: Despite the use of a glucose-free maintenance solution, plasma glucose concentration increased slightly but significantly 5 min after induction (5.3 ± 0.4 vs. 4.5 ± 0.4 mmol·L⁻¹, P < 0.05). This early increase corresponded to a significant increase in endogenous glucose production over basal conditions (4.1 ± 0.4 vs. 3.6 ± 0.2 mg·kg⁻¹·min⁻¹, P < 0.05), with no concomitant change in peripheral glucose utilization. Fifteen minutes after induction, both glucose utilization and production rates decreased steadily and were 20% less than basal values by 35 min after induction (2.9 ± 0.3 vs. 3.6 ± 0.2 mg·kg⁻¹·min⁻¹, P < 0.05). Similarly, glucose metabolic clearance rate decreased by 25% after 35 min. Despite the increase in blood glucose concentration, anesthesia resulted in a significant decrease in plasma insulin concentration.

Conclusions: These data suggest that halothane anesthesia per se affects glucose metabolism. The decrease in peripheral glucose utilization and metabolic clearance rates and the blunted insulin release question the relevance of glucose infusion in these clinical settings. (Key words: Anesthesia: halothane; Glucose: metabolism; production; utilization. Tracer dilution.)

SEVERAL studies have shown consistently that most patients¹–³ respond to halothane anesthesia and surgery with a significant increase in blood glucose, a change partly related to the simultaneous infusion of glucose-containing solutions.² Some investigators thus have advised that glucose-free solutions be used during surgery.³ On the other hand, the possibility that hypoglycemia may remain undetected during anesthesia has led to the recommendation for a routine use of glucose-containing solutions for perioperative fluid management.⁴ a conservative attitude in the absence of established glucose requirements.

However, intravenous glucose tolerance tests performed before and during halothane anesthesia prior to the beginning of surgery suggest that the increase in blood glucose concentration is not due only to the association of surgery and glucose infusion. Glucose fractional disappearance rate decreased by about one-third after induction,⁵ a decrease that is indicative of an imbalance between endogenous glucose production and glucose utilization but that does not allow to quantify their respective variations.⁶ Because it is the steady balance achieved between glucose utilization and glucose entry that ensures a stable plasma glucose concentration,⁷ it should be possible to avoid any detrimental variation in plasma glucose levels by closely adjusting glucose infusion rate to whole-body glucose uptake. Thus, we measured glucose utilization by peripheral tissues and endogenous glucose production before and during halothane anesthesia in adolescents, in an attempt to better characterize its effect on glucose metabolism and to evaluate its consequence on glucose requirements.
ANESTHESIA AND GLUCOSE METABOLISM

Subjects and Methods

Subjects

Eight patients entered the study, and measurements were completed for six of them (five boys, one girl). All patients required orthopedic surgery previously for the treatment of a limb fracture. After healing of the bone injury, they were scheduled for a second surgical procedure to remove the internal fixation devices used in the course of the first surgery. All patients were in good clinical condition (ASA physical status 1) at the time of the study. Their mean age (±SD) was 14.5 ± 2 yr, and study weight, 49.5 ± 4.5 kg, with a ratio of actual weight to expected weight-for-height of 1.03 ± 1.4. Patients requiring surgery for the treatment of acute bony or muscular injuries or with neurologic, cardiac, endocrine, or metabolic diseases were excluded from the study. This investigation was reviewed by the Necker-Enfants Malades Ethical Committee, and formal, informed consent was obtained from the patients and their parents.

Anesthesia

After basal measurements were completed (see below), anesthesia was induced with halothane in gradually increasing concentrations up to 3%. The trachea was intubated without the use of muscle relaxants, and anesthesia was maintained with halothane (mean end-tidal halothane concentration 1.19 ± 0.36%, RGM 5250 gas monitor, Ohmeda, Louisville, CO) and 60% N₂O in oxygen. Minute ventilation was adjusted to achieve an end-tidal carbon dioxide pressure ranging between 35 and 40 mmHg. Body temperature was measured by a thermistor probe inserted rectally and kept at 37°C by the use of a heating pad (Aquamatic K, Gorman-Rupp, Bellville, OH). Water and electrolytes were provided according to recommendations.¹⁰

Measurement of Glucose Utilization and Production

All patients were studied while in the postabsorptive state after an overnight fast (12 h). Basal glucose production and utilization were determined by the use of a primed, 2-h constant infusion (0.4 μmol·kg⁻¹·min⁻¹) of [6,6-²H₂]glucose,¹¹ 98%; CIL, Woburn, MA) through an indwelling butterfly needle placed in a forearm vein. Blood samples (1 ml) were drawn from a catheter placed into a contralateral forearm vein before and after 90, 100, 110, and 120 min after starting tracer infusion.

To determine the effects of anesthesia on glucose metabolism, the same tracer infusion went uninterrupted after induction, until the beginning of surgery, and blood samples (1 ml) were drawn every 5 min in the meantime. Blood was collected into heparinized tubes and centrifuged at 1,500 × g, +4°C for 5 min, and the plasma was stored at −30°C until analyzed.

Plasma glucose isotope ratios were measured by gas chromatography-mass spectrometry. Briefly, plasma samples (50 μl) were deproteinized with 1 ml of absolute ethanol and centrifuged at 6,500 × g, +4°C for 15 min, and the supernatant was applied onto an anion-exchange column (0.5 ml Dowex 1×8 – 0.5 ml Dowex 50W×8). Columns were washed with absolute ethanol, and glucose was eluted with 1 ml water. After evaporation to dryness, residues were dissolved in 50 μl of a 2% (weight/volume) solution of n-butylboron dihydroxide in pyridine and heated at 60°C for 1 h. After cooling, 50 μl acetic anhydride was added, and the screw-top vials were heated for 15 min at 60°C. Samples (2 μl) were injected into a 25 m × 0.32 mm CPSil 5CB capillary column (Chrompack, Middelburg, The Netherlands) by the use of a Ros injector. Glucose was eluted by using a temperature program (230–270°C, at a rate of 5°C·min⁻¹) and helium as a carrier gas. The column was directly fitted to the ion source of an INCOS 50 mass spectrometer (Finnigan Mat, Bremen, Germany) operated under positive electron impact ionization mode. Selected ion chromatograms were recorded at mass-to-charge ratios of 297 and 299. Glucose molar ratios were calculated from measured peak area ratios by using calibration curves obtained from the analysis of standards of known isotopic dilution. The rate of glucose appearance (Ra) and disappearance (Rd) were calculated by Steele’s equations in their derivative form¹²:

\[
Ra = \left[ i - (p \cdot V \cdot G(t) \cdot dZ/dt) \right]/Z(t),
\]

\[
Rd = Ra - (p \cdot V \cdot dG/dt),
\]

where i is the infusion rate of [6,6-²H₂]glucose, V the glucose distribution volume (assumed to be 26% of body weight),¹³,¹⁴ p the pool fraction (assumed to be 0.75),¹⁴ G the plasma glucose concentration, and Z the tracer-to-trace rate molar ratio.¹⁵ For the resolution of Steele’s equations, the time curves for glucose concentration and molar ratio were fitted by polynomial regression. The glucose metabolic clearance rate was obtained from the ratio of glucose utilization rate to plasma glucose concentration.

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Biochemical Assays

Plasma glucose concentration was measured by the glucose oxidase method,\textsuperscript{16} free fatty acids by colorimetric determination,\textsuperscript{17} and lactate by enzymatic determination.\textsuperscript{18} Plasma insulin and glucagon concentrations were determined by radioimmunoassay.\textsuperscript{19,20}

Statistics

Results are expressed as mean ± SD. Analysis of variance (ANOVA) for repeated measures was used to assess within-subject effects. When appropriate, the results obtained during anesthesia were further compared to basal conditions by using Dunnett's procedure. The level of significance was set at $P < 0.05$. All calculations were performed by the use of a standard BMDP program.\textsuperscript{21}

Results

There was a significant change in plasma glucose concentration during anesthesia (ANOVA $F_{2,55} = 8.3; P < 0.001$; fig. 1). Glucose concentration amounted to $4.5 \pm 0.3$ mmol·l$^{-1}$ before anesthesia, was increased to $5.3 \pm 0.4$ mmol·l$^{-1}$ ($P < 0.05$) $5 \text{ min after induction}$, and slowly decreased thereafter to $4.9 \pm 0.4$ mmol·l$^{-1}$ by 35 min. Plasma free fatty acid concentration did not significantly change ($0.762 \pm 0.47$ mmol·l$^{-1}$ $35 \text{ min after induction}$ vs. $0.653 \pm 0.4$ mmol·l$^{-1}$ before), whereas lactate concentration was increased ($1.1 \pm 0.3$ vs. $0.7 \pm 0.1$ mmol·l$^{-1}$ before; $P < 0.05$). Anesthesia resulted in a significant change in insulin concentration (ANOVA $F_{2,55} = 6.2; P < 0.001$; fig. 1). Plasma insulin concentration decreased from $14.5 \pm 3.8$ µU·ml$^{-1}$ before induction to $8.7 \pm 3$ µU·ml$^{-1}$ by 25 min ($P < 0.05$) and $9.2 \pm 3$ µU·ml$^{-1}$ by 35 min after induction ($P < 0.05$). Plasma glucagon also was less 35 min after induction ($129 \pm 31$ pg·ml$^{-1}$) than before anesthesia ($187 \pm 22$ pg·ml$^{-1}$; $P < 0.05$). Heart rate and systolic and diastolic blood pressures did not change significantly (table 1).

There were significant changes in both endogenous glucose production (ANOVA $F_{2,55} = 39.3; P < 0.001$) and glucose utilization (ANOVA $F_{2,55} = 22.5; P < 0.001$) during the study period. Before anesthesia, mean glucose turnover rate amounted to $3.62 \pm 0.23$ mg·kg$^{-1}$·min$^{-1}$. Five minutes after the induction of anesthesia, glucose production was increased to $4.1 \pm 0.4$ mg·kg$^{-1}$·min$^{-1}$ ($P < 0.05$; fig. 2). However, this increase in glucose production was short-lasting, be-

cause the value at 10 min after induction was comparable to basal production rate. In contrast, glucose utilization did not change significantly during the initial period of anesthesia. After 15 min, both glucose production and glucose utilization decreased by the same magnitude. Thirty-five minutes after the beginning of anesthesia, glucose turnover rate amounted to $2.9 \pm 0.3$ mg·kg$^{-1}$·min$^{-1}$, a value 20% less than before anesthesia ($P < 0.05$). Glucose metabolic clearance rate also decreased significantly (ANOVA $F_{2,55} = 8.6; P < 0.001$; fig. 3) and was 25% less than basal values by 35 min after induction ($P < 0.05$; fig. 3).

Discussion

The slight but significant increase in plasma glucose concentration observed after the induction of anesthesia in this group of adolescents is consistent with the changes previously observed in adults undergoing surgery under general anesthesia.\textsuperscript{1-5} In some studies, an increase in glucose concentration could be related to the simultaneous infusion of glucose-containing solutions.\textsuperscript{1,2} However, a definite increase in glucose concentration, though of smaller magnitude, also was detected in patients infused with glucose-free solutions.\textsuperscript{2,3} Although these studies provided indications that anesthesia and/or surgery alter the regulation of plasma glucose levels, they did not allow the possible effects of anesthesia to be differentiated from those of surgery. Because the current results were obtained before the

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beginning of surgery, they imply that halothane anesthesia per se may affect glucose metabolism, in agreement with previous reports suggesting that blood glucose levels could increase before the start of surgery.\textsuperscript{1, 3} This is also in keeping with animal experiments featuring a comparable response pattern of plasma glucose concentration during anesthesia alone.\textsuperscript{22}

Before anesthesia, glucose turnover and metabolic clearance rates were similar to those reported in post-absorptive normal subjects of comparable age.\textsuperscript{8, 11} In these conditions, the steady balance between hepatic glucose production and utilization by peripheral tissues ensured stable plasma glucose levels.\textsuperscript{8, 9} Under anesthesia, there was a significant change in mean glucose concentration 5 min after induction, although glucose utilization was still comparable to basal values. In contrast, there was a significant increase in endogenous glucose production at that time, suggesting that increased glucose concentration resulted from an early increase in glucose production with no concomitant change in glucose utilization by peripheral tissues. This view is consistent with animal experiments demonstrating that a steep increase in glucose production, with no change in peripheral glucose uptake, accounted for the early postinduction rise in plasma glucose concentration.\textsuperscript{22, 23} In addition to a possible stimulation of glycogenolysis by halothane,\textsuperscript{24, 25} this transient increase in endogenous glucose production could be related to the release of catecholamines.\textsuperscript{26}

Fifteen minutes after induction of anesthesia, glucose production and utilization decreased steadily, reaching values 20% less than baseline by the end of the study. This change is consistent with the 17–30% reduction in glucose turnover observed in anesthetized animals.\textsuperscript{22, 23, 27} Of major significance in these clinical settings is the decrease in glucose utilization by peripheral tissues. It is unlikely that it could be accounted for by the operation of the glucose-free fatty acid cycle,\textsuperscript{28} because free fatty acid concentration did not change significantly over the study period, in agreement with previous results.\textsuperscript{1} Decreased glucose utilization by the

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**Table 1. Mean Heart Rate and Systolic and Diastolic Blood Pressures before (Basal) and during Halothane Anesthesia**

<table>
<thead>
<tr>
<th></th>
<th>Basal</th>
<th>5 min</th>
<th>15 min</th>
<th>25 min</th>
<th>35 min</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>67 ± 10</td>
<td>71 ± 9</td>
<td>72 ± 8</td>
<td>70 ± 12</td>
<td>67 ± 9</td>
<td>0.10</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>110 ± 10</td>
<td>104 ± 9</td>
<td>105 ± 8</td>
<td>103 ± 10</td>
<td>105 ± 9</td>
<td>0.29</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>60 ± 6</td>
<td>56 ± 5</td>
<td>53 ± 10</td>
<td>56 ± 8</td>
<td>55 ± 5</td>
<td>0.57</td>
</tr>
</tbody>
</table>

Values are mean ± SD.

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**Fig. 2.** Changes in endogenous glucose production (Ra, circles) and peripheral glucose utilization (Rd, triangles) before and every 5 min during halothane anesthesia. Ra and Rd are expressed in percent change from basal values. The beginning of anesthesia is indicated by an arrow. Values are mean ± SD. *P < 0.05 versus basal values.

**Fig. 3.** Changes in glucose metabolic clearance rate before and every 5 min during halothane anesthesia. Metabolic clearance rate is expressed as percent change from basal values (4.4 ± 0.39 ml·kg\(^{-1}·\)min\(^{-1}\)). The beginning of anesthesia is indicated by an arrow. Values are mean ± SD. *P < 0.05 versus basal values.
brain was reported in animals under anesthesia. Although the reasons for such a change remain unclear, it could affect glucose turnover, because the human central nervous system represents 50–80% of basal whole-body glucose disposal after an overnight fast. On the other hand, a decrease in muscular activity would be an expected consequence of general anesthesia and could contribute to a significant glucose salvage, because muscle uptake accounts for about 20% of basal glucose utilization in postabsorptive adults. This is supported by results obtained in animals, showing a dramatic reduction of labeled 2-deoxyglucose uptake by postural muscles in anesthetized rats, as compared to awake animals, which reflects a significant decrease in total glucose uptake by these muscles under anesthesia. Thus, part of the reduction in peripheral glucose utilization in response to halothane anesthesia could be related simply to a decrease in the energy requirements of some tissues, a change that is consistent with the decrease in whole-body oxygen consumption observed in human adults and that questions the necessity of exogenous glucose infusion. Insulin concentration did not increase in response to the early increase in plasma glucose concentration displayed by our adolescent patients. Previous studies in adults showed that insulin response was inappropriate to the large increase in glucose concentration observed throughout anesthesia and surgery. Further observations demonstrated that halothane significantly blunted insulin responses to a glucose load, in contrast to the response during local spinal anesthesia. Similarly, halothane anesthesia induced a significant decrease in plasma insulin in fed rats, although halothane had no effect on the glucose-stimulated insulin release by isolated perfused pancreas. These results point toward a negative effect exerted by halothane on the regulation of insulin release. In our patients, this effect was substantiated by a significant decrease in insulin concentration, an alteration consistent with results obtained in dogs and further challenging the relevance of exogenous glucose infusion in these conditions.

The changes in glucose and insulin concentrations resulting from the use of halothane are reminiscent of results obtained with other general anesthetics. Intravenous glucose tolerance tests performed before and during methohexitone and isoflurane anesthesia before the beginning of surgery revealed a significant decrease in glucose fractional disappearance rate. A comparable decrease in glucose fractional disappearance rate also was noted after the intravenous administration of sodium thiopental. A decrease in glucose fractional disappearance rate is indicative of an imbalance between glucose production and glucose utilization, although it does not allow to quantify their respective variations, as would tracer dilution. This suggests that such alterations in glucose metabolism may not be specific to halothane anesthesia, a possibility supported by the comparable effects of halothane, isoflurane, and pentobarbital on glucose production and utilization and insulin release in animals. These results may further be relevant to older patients. Indeed, the decrease in glucose fractional disappearance rate in response to halothane indicates that its use results in an imbalance between glucose production and utilization also in adults. Whether this may apply to infants or small children cannot be ascertained from this study.

Thus, an early increase in endogenous glucose production without a concomitant increase in peripheral glucose uptake likely accounts for the rise in blood glucose concentration observed in these adolescents during halothane anesthesia, despite the infusion of a glucose-free maintenance solution. Most importantly, the subsequent decrease in peripheral glucose utilization and glucose metabolic clearance rates questions the relevance of glucose infusion in these clinical settings, because a significant hyperglycemia eventually would result from exogenous glucose intake in excess of peripheral glucose utilization. This hyperglycemic response would be exacerbated by the blunted insulin response, reducing any adaptive change in peripheral glucose uptake with glucose infusion. Thus, the routine use of glucose-containing maintenance solutions in adolescents may not be advisable during halothane anesthesia, because it would induce an overt imbalance between total glucose entry (from endogenous sources) and glucose disposal rates.

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