Somatostatin prevents the postoperative increases in plasma amino acid clearance and urea synthesis after elective cholecystectomy

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Abstract

The importance of glucagon on postoperative changes in hepatic amino-nitrogen conversion were investigated in six patients undergoing elective cholecystectomy for uncomplicated gall stones. Patients were given infusions of somatostatin (bolus of 6 µg/kg followed by continuous infusion of 6 µg/kg/h) from induction of anaesthesia to the end of investigation, the first postoperative day (30 hours). Controls were 16 patients undergoing the same procedures omitting the somatostatin infusion. In all patients blood concentration and plasma clearance of total α-amino-nitrogen, and amino acid stimulated rate of urea synthesis were measured. Elective cholecystectomy decreased blood α-amino-nitrogen concentration from mean (SEM) 2·9 (0·2) to 2·4 (0·1) mmol/l (p<0·05), increased the clearance of total α-amino-nitrogen from 5·2 (0·3) to 6·6 (0·3) ml/s (p<0·05), and increased the rate of amino acid stimulated urea synthesis from 27 (1) to 37 (2) µmol/s (p<0·05) pointing to increased hepatic removal of amino-nitrogen at expense of plasma amino-nitrogen. Infusion of somatostatin prevented increase of glucagon for 24 hours after surgery, and prevented the negative changes in postoperative nitrogen homeostasis resulting from the postoperative changes in hepatic nitrogen conversion, suggesting glucagon as mediator. The exact mechanism remains in doubt, however, because of the multiple effects of somatostatin.

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Keywords: somatostatin, urea synthesis, cholecystectomy, amino acid clearance.

Regulation of postoperative loss of body protein is not fully understood. The liver plays a primary part in the catabolic stress response after surgery. The hepatic effectiveness of conversion of plasma amino-nitrogen into urea nitrogen increases considerably (more than tissue amino-nitrogen release), so that the plasma amino-nitrogen decreases because of the depletion by the liver.[1][2] This phenomenon is a consistent response to cholecystectomy.

Many possible regulators has been proposed.[3–8] The 'traditional' catabolic hormones (glucagon, cortisol, and catecholamines) are established mediators.

Both glucagon and cortisol stimulate urea synthesis,[9–11] and combined hormonal-neural blockade of these hormones returned postoperative changes in hepatic amino-nitrogen conversion to normal values.[12] The aim of this study was to investigate the effect of glucagon on these changes by determination of amino-nitrogen clearance and urea synthesis during infusion of somatostatin.

Methods

Patients

The experimental group comprised six patients (one male and five females) with uncomplicated gall bladder stones verified by ultrasonography. Their average age was 42 years (range 23–58) and body weight 67 kg (range 62–98). Controls were 16 patients (6 males and 10 females) reported previously[12] with an average age of 42 years (range 34–59) and body weight of 77 kg (range 55–92). None of the patients had any other known disease. There was no difference in the duration in the surgical procedure or maximum postoperative temperature between the two groups.

The subjects gave their informed consent, and the protocol was in accordance with the declaration of Helsinki II and was approved by the local committee of ethics.

Surgical procedures

The patients were sedated with benzodiazepine (Apozepam) 5–10 mg and anaesthetised with low dose fentanyl-droperidol and N_2O_2. Cholecystectomy was performed by a laparotomy through a subcostal incision. The intra and postoperative course was uncomplicated in all cases, and without exploration of the common bile duct. No blood transfusion was given.

Protocol

Each subject was their own control. They were investigated twice on the day before surgery after a nine hour fast with free access to tap water, and on the first postoperative day 26 hours after skin incision. Each investigation consisted of a prime continuous infusion into an antecubital vein[1] of a mixture of amino acids (Pfrimmer, Erlangen, Germany), measured to be free from urea and ammonia. This established a steady state both with respect to blood amino acid concentration and hepatic amino-nitrogen conversion as assessed

TABLE I *Concentrations of total α-amino-nitrogen (AAN mmol/l) and glucose (mmol/l) before and after cholecystectomy in both groups fasting and during amino acid infusion*

	Before		First postoperative day	
	Fasting	AA load	Fasting	AA load
AAN (mmol/l)				
Control	2·9 (0·2)*¶	5·0 (0·2)†¶	2·4 (0·1)*¶	3·9 (0·3)‡¶
Somatostatin	2·5 (0·3)‡¶	4·6 (0·5)§¶	4·1 (0·5)‡¶	5·8 (0·5)§¶
Glucose (mmol/l)				
Control	4·6 (0·1)‡	4·8 (0·1)§	5·7 (0·3)‡	5·6 (0·3)§
Somatostatin	5·1 (0·1)‡	5·5 (0·1)§	6·5 (0·4)‡¶	7·1 (0·6)§¶

*, †:Significant decrease before *v* after fasting and AA load; ‡, §: significant increase before *v* after fasting and AA load; ¶: significant increase during AA infusion. Data presented as mean (SEM).

by the rate of urea synthesis. The priming consisted of an infusion of amino-nitrogen at a rate of 41·2 μmol min⁻¹kg⁻¹ body weight for 60 minutes, and the continuous infusion of an infusion for 180 minutes at a constant rate of 22·3 μmol min⁻¹kg⁻¹ body weight.[1] The amino acid infusion resulted in a total fluid volume of 500 ml.

Venous blood samples were drawn from the contralateral arm before start of the amino acid infusion and then every half hour.

Urine was collected quantitatively by voiding from the time when the amino acid infusion was started and every hour during infusion.

After the preoperative investigation, patients had free access to tap water and received for the rest of the day a diet containing 2000 kcal and 75 g of protein. On the day of operation the patients received 2000 ml of isotonic saline intravenously, and on average 2500 ml of isotonic saline during the operation.

During the amino acid infusions no other infusion was given.

The patients in the experimental group received, in addition, a hormonal blockade started during induction of anaesthesia and maintained until the end of investigation – that is, for 30 hours after skin incision. Both groups received morphine intramuscularly, 10 mg every six to eight hours for relief of pain.

Blockade

Natural somatostatin (SS28) (DuraScan Medical Products A/S, Denmark) was given as a bolus injection of 6 μg/kg⁻¹ followed by a continuous infusion of 6 μg/kg/h dissolved in isotonic saline.

There was no undesirable effect of the blockade concerning change in blood pressure, heart rate, or blood glucose.

Analyses

Total α-amino-nitrogen concentration in plasma and urine was determined by the dinitroflourobenzene method[13] (coefficient of variation of analysis 1·25%) and urea in blood and urine by the Urease-Berthelot method[14] (coefficient of variation 1%). Blood glucose concentration[15] was determined by a glucose oxidase method.

Plasma insulin and glucagon concentrations were determined by radioimmunoassay.[16][17] Plasma cortisol concentration was determined by high pressure liquid chromatography.[18]

Calculations

Elimination of infused amino-nitrogen was quantified by the plasma clearance (ml/s), calculated as infusion rate divided by average plasma concentration during steady state.

The urea nitrogen synthesis rate (UNSR) (μmol/s) was calculated as urinary excretion rate of urea (E) corrected for accumulation of urea (A) in the total body water and fractional gut hydrolysis (L):

$$UNSR = (E+A)/(1-L)$$

The total body water (TBW) was estimated from body weight (BW, kg), body height (BH, cm), and age (Y, years), by the formulas[19]:

$TBW = 0·3265BW + 0·2239BH - 0·138Y - 14·47$ for men and
$TBW = 0·2363BW + 0·1962BH - 0·0272Y - 10·26$ for women.

L was taken to be 17%.[20]

The nitrogen exchange during steady state was calculated as the percentage of infused amino-nitrogen appearing as urea nitrogen by excretion plus accumulation.

Statistical analysis

Values are given as mean (SEM). Difference between groups was evaluated by two tailed *t* tests of means or pairs as appropriate. p Values smaller than 0·05 were considered statistically significant.
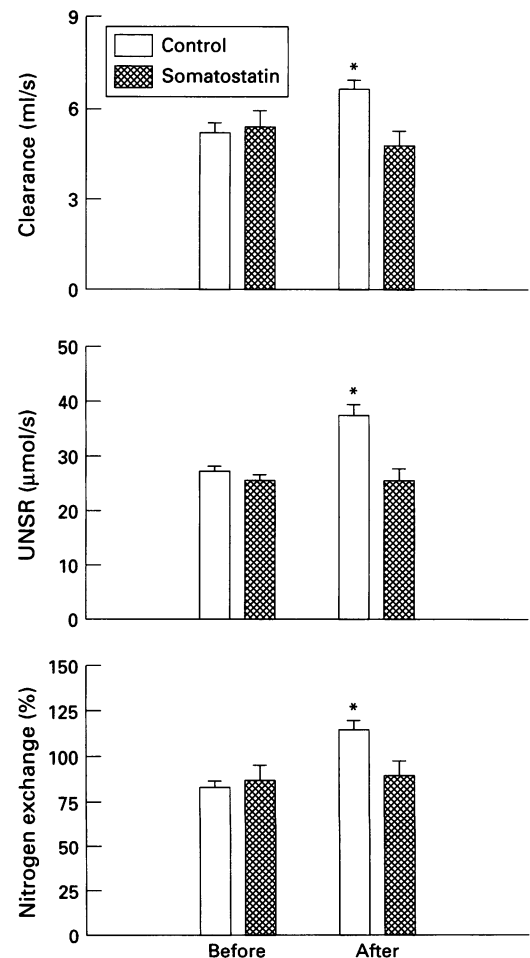

Figure 1: Total α-amino-nitrogen clearance, rate of urea nitrogen synthesis rate (UNSR), and nitrogen exchange during amino acid infusion in the control group (open bars) and the somatostatin treated group (hatched bars) before and after the operation. *Significant increase p<0·05.

Results

Amino-nitrogen

The amino acid infusions increased the fasting plasma concentrations of total α-amino-nitrogen by about 80% (Table I). Postoperatively, the amino acid concentrations were about 20% lower in control patients (p<0·05), and 60% (fasting) and 25% (amino acid load) higher in the patients with blockade (p<0·01) (Table I).

Postoperatively, the plasma clearance of total α-amino-nitrogen increased by about 25% in the control group (p<0·05), and did not change in the blockade group (Fig 1).

Urea synthesis

In the control group, surgery increased the amino acid stimulated rate of urea synthesis by one third (p<0·05). In the blockade group, surgery did not change the rate of urea synthesis (Fig 1).

Preoperatively, 15% of the infused amino-nitrogen was retained in the body, and postoperatively in the control group 15% more was excreted than infused (p<0·02). The blockade prevented this postoperative loss of amino-nitrogen (Fig 1).

Glucose

Surgery increased fasting blood glucose concentration by 25% (p<0·05) in the control group, without further increase during amino acid load (Table I). In the blockade group surgery increased the fasting concentration by 30% (p<0·05), and the amino acid load increased it further by 10% (Table I).

Hormones

Glucagon – preoperatively, the amino acid infusion increased plasma glucagon concentration by about 40% over fasting in both groups (p<0·02). Postoperatively, glucagon more than doubled (p<0·001) in the control group, while it remained unchanged in the blockade group (Table II). Postoperatively, the fasting value was 70% (p<0·05) higher than preoperatively in the blockade group. Somatostatin halved glucagon concentration for 12 hours after start of operation (Fig 2) (p<0·05),
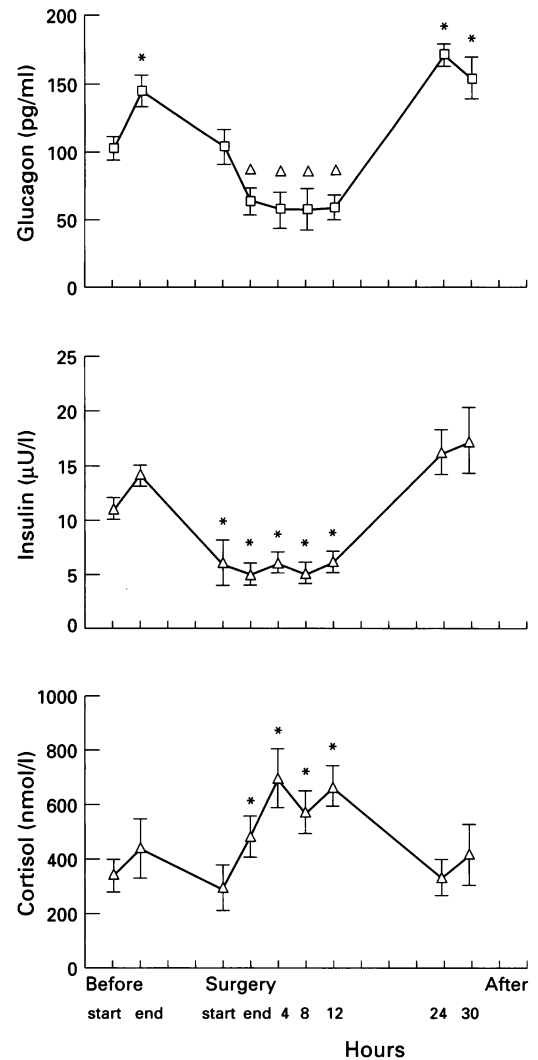

Figure 2: Plasma concentrations of glucagon (increase (*) and decrease (△), p<0·05), insulin (decrease (*), p<0·05), and cortisol (increase (*), p<0·05) during the investigation period in the somatostatin treated patients.

whereafter the concentration rose to the preoperative value during amino acid load.

Insulin – preoperatively, the amino acid load did not change insulin in both groups, but doubled it after surgery (p<0·001) in controls, while it remained unchanged in the blockade group. In the blockade group insulin was halved (p<0·05) for 12 hours after which it rose to preoperative values (Table II, Fig 2).

Cortisol – surgery increased fasting cortisol by 75% (p<0·05) and the amino acid load decreased it by 25% (p<0·05) postoperatively in controls. In the blockade group cortisol doubled from four to 12 hours after surgery, but was normal after 24 hours (Table II, Fig 2).

Discussion

Somatostatin prevented the hepatic catabolic response to cholecystectomy.

The increase in the control group of urea synthesis at lower amino acid concentration after surgery reflects changes in liver function with regard to amino-nitrogen disposal – that is, more urea was synthesised and more amino-nitrogen was lost for protein synthesis.

TABLE II *Plasma concentrations of glucagon (pg/ml), insulin (μU/l), and cortisol (nmol/l) before and after cholecystectomy in both groups fasting and during AA infusion*

	Before		First postoperative day	
	Fasting	AA load	Fasting	AA load
Glucagon (pg/ml)				
Control	92 (6)*	128 (10)*	107 (9)†	226 (13)†
Somatostatin	100 (9)*,‡	142 (12)*	167 (8)‡	150 (15)
Insulin (μU/l)				
Control	15 (2)	15 (2)	19 (2)†	40 (6)†
Somatostatin	11 (1)	14 (1)	16 (2)	17 (2)
Cortisol (mmol/l)				
Control	288 (34)‡,§	226 (21)§	503 (56)‡,¶	399 (57)¶
Somatostatin	348 (57)	443 (109)	333 (66)	416 (152)

*†Significant increase during AA load before and postoperatively; ‡significant increase of fasting values; §¶significant decrease during AA load before and postoperatively. Data presented as mean (SEM).

Postoperatively, glucagon, cortisol, and catecholamine concentrations increased. Glucagon directly increases the hepatic efficacy for urea synthesis,[9][10] and cortisol increases the capacity of urea synthesis in rats[11] and acts permissively for the effects of glucagon on urea synthesis.[21] Catecholamines have no effect in themselves on urea synthesis[22] but seem to act permissively for the effects of cortisol.[23] Prostaglandins interact with the catabolic hormones and accelerates the hepatic catabolic response.[24-26] Cytokines seem to accelerate hepatic synthesis of acute phase proteins[27] and increase plasma glucagon and cortisol to concentrations as seen after stress.[28][29] Other hormones such as human growth hormone[7] and anabolic steroids[30] have been shown to improve postoperative nitrogen economy, but it is not known whether the effects of these hormones entail changes in liver function.

Somatostatin blocks pancreatic release of glucagon and insulin.[31] The postoperative time course of glucagon was not measured in the control group, but has been shown to increase 12–24 hours after surgery.[1][2][32][33] Infusion of somatostatin returned to normal the expected increases of glucagon. Also insulin decreased postoperatively during the blockade. If anything, however, insulin decreases the capacity for urea synthesis in rats,[34] and seems to have no effect on hepatic nitrogen conversion in humans.[35] Apart from these changes, cortisol increases within hours after induction of anaesthesia, and may stay increased for up to one week after surgery depending on the severity of the stress induced.[2][36][37] Somatostatin did not influence the increase of cortisol during 12 hours postoperatively, but returned to normal the increase seen in the control group 24 hours postoperatively. The return to normal values of the increase in hepatic nitrogen conversion by somatostatin may therefore be caused by changes in both glucagon and cortisol. As the time course of the effect of somatostatin on the two hormones are different, this might show that both the preceding hormonal milieu and the actual hormonal concentrations during the investigation may be of importance. In perfused rat livers the catabolic hormones only increase the hepatic conversion of amino-nitrogen in livers from previously (three hours) operated rats,[28] showing that these changes depend more on the preceding hormonal milieu shortly after surgery than on the actual concentration during the investigation.

In an earlier study, we prevented the catabolic response to upper abdominal surgery in humans by combined hormonal-neural blockade, ameliorating the postoperative increases of glucagon, cortisol, catecholamines, and afferent responses from the wound.[12] The blockade with somatostatin alone resulted in the same normalisation of the postoperative hepatic amino-nitrogen conversion, suggesting that glucagon directly or indirectly is of importance for the postoperative increase in hepatic amino acid conversion.

Triple infusion, however, of the traditional catabolic hormones (glucagon, cortisol, and catecholamines) to healthy humans only elicits a catabolism that is much less severe than in postoperative situations,[3-5] suggesting that other factors are also important. Cytokines (tumour necrosis factor, interleukin 1 and 6) are among the prime candidates. Infusion of these cytokines, as just one of numerous other effects, reproduces the increased concentrations of both glucagon and cortisol as measured after surgery.[27-29] This suggests that the cytokines either initiate or comediate the postoperative change in nitrogen homeostasis by changes in the traditional catabolic hormones. The effect of somatostatin infusion on the cytokine response is not known but the blockade may modify hormonal changes secondary to cytokine stimulation. Somatostatin also inhibits the release of several gastrointestinal peptides such as gastrin, secretin, cholecystokinin, vasoactive intestinal peptide, and pancreatic polypeptide.[38][39] However, any influenze of these hormones on urea synthesis has never been shown. Furthermore, somatostatin reduces hepatic blood flow by 12–25%,[40][41] which may contribute to down regulate hepatic amino-nitrogen conversion, but such changes cannot account for the total effect of somatostatin.

The increased urea synthesis shows that the decrease in amino-nitrogen concentration after surgery was mainly the result of removal by the liver. This is primarily caused by decreases of the gluconeogenic amino acids alanine, arginine, glutamate, glycine, proline, serine, and the two essential amino acids lysine and threonine.[1][2]

The slight postoperative hyperglycaemia is caused by increased gluconeogensis[42] and peripheral insulin resistance[43] and was not affected by the blockade. Glucose suppresses urea synthesis mainly by decreasing glucagon,[44] and spares some nitrogen postoperatively[45], but the effect is limited by the insulin resistance.[42] The normalisation of the hepatic amino-nitrogen conversion during the blockade and the relative hypoinsulinaemia is, therefore, not explained by the hyperglycaemia.

In conclusion, our study shows that the negative changes in postoperative nitrogen homeostasis resulting from increased hepatic efficacy for urea synthesis are preventable by somatostatin infusion. This suggests glucagon as a mediator. The exact mechanism of the inhibition remains uncertain, however, because of the multiple effects of the somatostatin infusion. A possible clinically beneficial effect of somatostatin in this situation awaits further studies.

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