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Corticotropin-releasing factor is present in intestinal tissue of patients with gastrointestinal dysfunction following shock and abdominal surgery

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ABSTRACT

Objective: Corticotropin-releasing factor (CRF) is implicated in stress-related gastrointestinal dysfunction, possibly causing gut dysfunction following trauma and surgery. We investigated plasma and intestinal tissue CRF levels and gut function in patients with traumatic shock or those undergoing elective abdominal surgery.
Research methods and procedures: In a prospective, parallel, observational study in a university hospital surgical intensive care unit (ICU), 8 shocked patients (systolic blood pressure <90 mmHg and/or acidosis and/or urine output <1 mL/kg/hr and/or requiring >2 L of intravenous fluid resuscitation) undergoing small bowel resection during emergency laparotomy following abdominal injury and 17 stable patients undergoing elective hepatobiliary surgery were included if they required postoperative ICU management. Serial plasma and intestinal CRF was measured and postoperative gastric emptying and intestinal permeability were evaluated.
Results: Plasma CRF was significantly increased in the shocked patients compared with the elective surgery patients at all times. CRF peptide was quantified in intestinal tissue at similar levels in both groups. Intestinal permeability was increased and associated with shock and resuscitation fluid volume. Gastric emptying was retarded and correlated significantly with shock but not with plasma CRF. Delayed gastric emptying in shocked patients was associated with longer ICU stay.
Conclusions: The novel finding is the presence of CRF in the small bowel of both elective and emergency gastrointestinal surgery patients with concomitant gastrointestinal dysfunction. Circulating CRF is associated with poor gastric emptying, which prolongs ICU stay, whereas shock significantly impairs gastric emptying and gut permeability.

Introduction

Certain patterns of gut dysfunction, including diarrhea, poor gastric emptying, and enhanced intestinal permeability are well recognized phenomena in critically ill patients, especially following circulatory shock [1–3], but the underlying causes of gut dysfunction in the critically ill have not been well elucidated. In particular, what is not completely clear is the identity of those molecules and mediators responsible for inducing these dysfunctional changes in gut physiology. Corticotropin-releasing factor (CRF) has emerged as a leading mediator in functional bowel disorders and in the effects of stress and inflammation on the gastrointestinal tract [4,5]. Beyond its established role in the hypothalamic-pituitary-adrenal (HPA) axis, CRF may be synthesized in colonic mucosa. More recent data has shown that it probably plays an important role as a mediator in the gut-related physiological changes which occur with stress [6–9].

It was therefore the aim of this study to determine whether CRF is present in stressed human small bowel and whether plasma and gut tissue CRF levels were associated with markers of shock, gastric emptying time, and intestinal permeability.

Materials and methods

Patients

In this prospective, investigational, clinical study, adult patients with penetrating traumatic abdominal injury due to gunshot or stab wound and shock (defined as systolic blood pressure <90 mmHg and/or acidosis and/or urine

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Table 1
Demographic and baseline characteristics—mean (SD)

	Trauma group (n = 8)	Elective group (n = 17)	*P* value
Age (years)	28.1 (9.8)	50 (9.9)	<0.0001
Gender distribution m/f	8/0	10/7	0.032
Diagnosis	Penetrating abdominal trauma due to gunshot wound (8 pts)	Bile duct obstruction/ injury (4 pts) Pancreatic lesion (8 pts) Chronic calcific pancreatitis (5 pts)	
Surgical procedure	Laparotomy with various repairs of internal injuries, including small intestinal resection and primary anastomosis (8 pts) *2 patients also underwent subxiphoid window which progressed to sternotomy (1 pt)*	Hepaticojejunostomy and enteroanastomosis (7 pts) Whipple's procedure (4 pts) Gastrojejunostomy and enteroanastomosis (3 pts) Choledocotomy, cholecystojejunostomy/ choledocojejunostomy and roux loop enteroanastomosis (2 pts) Pancreaticojejunostomy and enteroanastomosis (1 pt)	
APACHE II score (first 24 hours in ICU)*	7.5 (5.5)	7.25 (5)	0.9
Injury severity score (ISS)	26.5 (20–37)†	NA	
Patients receiving postoperative mechanical ventilation (n (%))	4 (50%)	1 (6%)	0.01
Time between injury and hospital arrival (min)	183 (118)	NA	
Time between injury and surgery (min)	388 (153)	NA	
Minimum baseline systolic blood pressure (mmHg)	76 (27)	NA	
IV fluids administered in first 24 hours (mL)	11450 (3728)	5479 (1842)	0.00001
Duration of surgery (min)	189 (36)	266 (115)	0.08

* APACHE II: Acute physiology and chronic health evaluation.
† Median (IQR).

output <1 mL/kg/hr and/or the need for >2 L of intravenous fluid resuscitation) admitted to a Level 1 Trauma Unit within 12 hr of injury and requiring emergency laparotomy with surgical resection of small bowel and postoperative intensive care unit (ICU) admission were compared with a stable, elective surgery group undergoing hepatobiliary surgery involving small bowel resection and requiring elective postoperative admission to ICU. For both groups, exclusion criteria were age less than 18 yrs, pregnancy/lactation, known inflammatory bowel disease, a laparotomy finding of previous intestinal resection, requirement for partial/ total gastrectomy, the clinical judgment that survival beyond 24 hr was extremely unlikely, and lack of informed consent. Approval of the study was granted by the Human Research Ethics Committee of the University of Cape Town Health Sciences Faculty (ref 358/2003). Informed consent was obtained from elective patients and deferred consent from the trauma patients.

Procedures

Plasma CRF levels in blood were measured prior to induction of anesthesia, at the time of surgical resection of bowel, and on the first postoperative day using a using a commercial RIA kit (corticotropin-releasing factor [CRF], human, RIA kit, Phoenix Pharmaceuticals Inc, Burlingame, CA, USA). Discarded but undamaged resected full-thickness small bowel tissue was assayed for CRF peptide after an acidification, homogenization, and protein extraction procedure using a commercial RIA kit (corticotropin-releasing factor [CRF], human, RIA kit, Phoenix Pharmaceuticals Inc, Burlingame, CA, USA). Tissue CRF was quantified with reference to tissue total protein levels, which were assayed using a commercial colorimetric protein assay kit (BCA™ Protein Assay Kit, Pierce, Rockford, IL, USA) and the CRF results were expressed as a percentage of total protein. Gastric emptying rate was measured on the first postoperative day using a standard 3-hr paracetamol absorption test in which 1500 mg paracetamol was delivered via a nasogastric tube, which was then clamped [10]. Intestinal permeability was tested on the first postoperative day using the lactulose-mannitol absorption and urinary excretion test. This technique used high-pressure liquid chromatography on an accurately measured 6-hr urine collection relative to a baseline urine sample, after 10 g lactulose and 5 g mannitol were delivered in 50 mL tap water via the nasogastric tube, which was then clamped [11]. Prior to both tests, patients fasted and prokinetic drugs and paracetamol were withheld for 24 hr.

Table 2
Outcome variables—mean (SD)

	Trauma group (n = 8)	Elective group (n = 17)	*P* value
ICU days	3 (3.0)	1.9 (1.2)	0.2
Ventilator days	1.37 (1.8)	0.06 (0.24)	0.007
Number of reoperations	0.62 (1.1)	0 (–)	0.036
Number of nosocomial infections	1.25 (1.0)	0.47 (0.7)	0.038
Hospital days	16.25 (11)	13.2 (4.5)	0.3
Predicted risk of mortality (%) based on injury severity score	15 (6–41)*	NA	
Hospital mortality—lived/died	7/1	17/0	0.14

* Median (IQR).

Statistical analysis

The sample size required with a power to detect a 20% intergroup difference in CRF levels, setting the alpha error at 0.05 and the beta error at 0.2, was found to be seven patients per group, assuming the standard deviation was equal for both groups. Data was checked for normality of distribution and was reported as median (interquartile range) when nonparametric and mean (standard deviation) when normally distributed. Between-group differences were tested using the independent *t*-test or the Mann–Whitney test, as applicable, for the distribution of the data. The CRF levels at the different times and the changes from the baseline within and between groups was tested by repeated measuring via Analysis of Variance (ANOVA). Two-way factorial ANOVA was used to measure intergroup differences in physiological tests and clinical indicators. For significant ANOVA models, post hoc testing was done using Tukey's Honest Significant Difference test. Secondary analysis included correlations using Pearson's product-moment or Spearman's correlation test as applicable. Statistical significance was taken as a *P* value of <0.05 in all cases. Results with a *P* value of <0.1 were considered to be trending toward statistical significance. Analysis was performed using Statistica 9 (Statsoft, Tulsa, OK, USA).

Results

Seventy-five patients were excluded because they failed to meet predefined inclusion criteria. Twenty-eight patients did not have bowel resection, 15 did not consent, 14 were not shocked, 4 were underage, 2 died prior to enrollment, and 12 had other exclusions. Data from 25 of 100 screened patients was included: 8 trauma patients and 17 elective surgery patients. The demographic and clinical data and surgical procedures are listed in Table 1. No patients had liver or renal failure at the time of testing. Trauma patients were significantly younger and required more perioperative intravenous fluids than elective patients. The outcome variables for the two groups are summarized in Table 2.

The group median (IQR) values for plasma CRF are shown in Table 3. Plasma levels of CRF at all three times were markedly raised above the reference range in the trauma group and were marginally raised in the elective group, but with no statistical difference between the CRF levels of the different sampling times