Role of actin cytoskeleton in deoxycholate (DC) induced gastric mucosal cell death

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INTRODUCTION: We have previously shown that apoptosis is the major cause of gastric mucosal cell death induced by DC, and is characterized by activation of initiator caspases 8 and 9, downstream activation of effector caspases 3 and 6, and subsequent disassembly of the cell. This study was undertaken to determine whether disassembly of actin was linked with gut injury using DC, and whether caspase cascade inhibition could maintain cytoskeletal integrity.

METHODS: AGS cells (human gastric mucosal cell line) received no pretreatment or were preincubated with caspase inhibitors for 30 minutes. Cells were then treated with DC (300 micromolar; a physiologically relevant concentration) and incubated for 1 hour. Cells were subsequently fixed, permeabilized, and incubated with Hoechst dye and rhodamine-phallodin to visualize the nucleus and F-actin microfilaments.

RESULTS: Results showed that actin morphology determined shape and size of cell changes. In response to DC there was collapse and shrinkage of cells. Caspase-3 and caspase-6 inhibitors partially restored DC-induced microfilament collapse. The most effective protection, however, resulted from z-VAD (a pan-caspase inhibitor) pretreatment which blocked the entire caspase cascade and prevented DC induced membrane and cytoplasm disruption and restored the F-actin ring.

CONCLUSIONS: We conclude that cell death induced by DC is associated with breakdown of the actin cytoskeleton. Because caspase inhibition can prevent this disassembly, our results suggest that the cytoskeleton is a major target for cell disassembly during apoptosis.

Does resection of pancreas cancer have a palliative effect? Longterm appraisal of readmissions

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INTRODUCTION: The palliative benefits of pancreaticoduodenectomy (PD) for pancreas cancer remain largely unknown; information regarding long-term readmission rates and reasons for readmission is scarce. Given the low cure rate following PD in resectable pancreas cancer, this study attempts to investigate the palliative effects of PD by examining long-term follow-up, specifically, the number and reasons for readmission.

METHODS: California Cancer Registry (1994-2004) was linked to the Inpatient file; patients with pancreatic adenocarcinoma who had undergone PD were identified, excluding 30-day mortality. All hospital readmissions after PD were analyzed with respect to admission diagnoses.

RESULTS: Of 2,148 patients who underwent PD for pancreas cancer, 82% were followed until death; median follow-up of survivors was 44 months. Perioperative mortality was 6%. There were 4,258 readmissions; 23% of the cohort was never readmitted. Diagnoses associated with readmission included dehydration/malnutrition (27%), anemia (21%), and sepsis (15%). Gastrointestinal and biliary obstruction were associated with 10% and 6% of readmissions. Abdominal pain was associated with 2% of readmissions.

CONCLUSIONS: Overall, readmissions after PD for pancreas cancer were lower than expected given the usual progression of disease. Approximately 1/3 of admissions were due to malnutrition/dehydration and were potentially avoidable with institution of palliative care services along with patient education. Interestingly, 23% of the cohort was never readmitted to the hospital following PD and only 2% of admissions had a component of abdominal pain as reason for admission. This may be evidence for the palliative effect of PD in the setting of adenocarcinoma of the pancreas.

Role of vagal fibers in post-transcriptional regulation of intestinal sodium-glucose cotransporter expression

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INTRODUCTION: Rodents display rapid and anticipatory diurnal rhythms in brush-border sodium-glucose cotransporter-1 (SGLT1) expression. We have used this novel model to study regulation of intestinal transporters. We aimed to identify the role of selective vagal fibers in regulating SGLT1 expression.

METHODS: Male Sprague-Dawley rats were randomized to laparotomy and either total subdiaphragmatic vagotomy, deafferentation with 1mg capsaicin applied to the vagus or sham procedure. Postoperatively, the animals were maintained under 12-hour light cycles with ad lib food at night only, and harvested on the 10th day (n=4-6 per arm) at four time points: ZT3, ZT9, ZT15 and ZT21 (ZT0=lights-on). Jejunal mucosa was retrieved by scraping. Protein was quantified by Western immunoblotting and densitometry relative to actin, and mRNA by quantitative-PCR relative to GAPDH. Fluorogold neuronal tracer was used to confirm complete disruption in vagotomized animals and integrity of the vagus in the other groups.

RESULTS: There was persisting diurnal rhythmicity in mRNA in all cohorts, peaking at ZT9 ($p<0.01$). At protein level, sham animals displayed rhythmicity in SGLT1 ($p=0.018$) expression, peaking at ZT15. This was abolished by total vagotomy ($p=0.74$) and deafferentation ($p=0.93$).

CONCLUSIONS: Diurnal rhythmicity in SGLT1 transcription is vagally-independent. But total vagotomy or disruption of afferent vagal fibers led to dissociation of the protein rhythm, suggesting a post-transcriptional role in SGLT1 expression. The vagal afferents play a role in the feedback loop regulating post-transcriptional con-

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