The studies were of adequate quality. Erythromycin prior to endoscopy in UGIB demonstrated a statistically significant improvement in visualization of the gastric mucosa (OR 4.89; 95% CI: 2.85-8.38, p<0.01) and decrease in the need for a second endoscopy (OR 0.42; 95% CI: 0.24-0.74, p<0.01). A trend was noted for less units of blood transfused (WMD -0.48; 95% CI: -0.97-0.01, p=0.05) with erythromycin as compared to no erythromycin. No publication bias or significant heterogeneity was noted for all outcomes. Conclusion: Erythromycin infusion prior to endoscopy in acute UGIB significantly improves visualization of gastric mucosa while decreasing the need for a second endoscopy. Based upon these results, erythromycin should be strongly considered prior to endoscopy in patients with UGIB.

112

Mortality From Acute Upper Gastro-Intestinal Bleeding in the UK - Does it Display a "Weekend Effect"?

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INTRODUCTION Several medical and surgical conditions demonstrate an association between presentation to hospital at the weekend and increased mortality.Potential reasons for this "weekend effect" include reduced staffing levels and a lower likelihood to undergo invasive procedures.Acute Upper Gastrointestinal Bleeding(AUGIB)is an ideal condition to examine weekend/weekday mortality as it has substantial mortality (10%) and may require early access to upper endoscopy to achieve haemostasis.A recent UK nationwide audit of patients admitted with AUGIB revealed that the majority of AUGIB patients (59%) present out of hours and only half of UK hospitals have a formal out of hours endoscopy service. AIMS AND METHODS To analyse whether weekend presentations for AUGIB have a higher mortality compared with those patients presenting on weekdays.Further analyses were performed on patients included in the 2007 UK Comparative Audit of Upper Gastrointestinal Bleeding and the Use of Blood.In this study prospective data were collected electronically on consecutive patients presenting to all UK hospitals with AUGIB between 1st May-30th June 2007.Weekend presentation was defined as any patient presenting between midnight on Friday through to midnight on Sunday. RESULTS Data were analysed on 6750 patients across 208 UK hospitals,including both new admissions with AUGIB (5550/6750) and existing in-patients (1107/6750).Patient characteristics were comparable with no significant difference between mean Rockall score at presentation,mean number of co-morbidities,receipt of red cell transfusion, therapeutic endoscopy for actively bleeding lesions,length of hospital stay and surgery.The only notable difference was that a significantly smaller percentage of patients were endoscoped either within 12 or 24 hours on the weekend.Despite this delay to earlier endoscopy there was no significant difference in mortality between patients presenting on the weekend (9.9%) or during the weekdays (10%).A subanalysis of new admissions only with AUGIB similarly showed no difference in mortality for weekend (7%, 86/1228) versus weekday (6.8%, 293/4321) presentation. CONCLUSIONS In this large nationwide UK audit,we found no overall difference in mortality in patients presenting with AUGIB on weekends as compared with those presenting on weekdays, regardless of whether they were new admissions or in-patients at the time of their bleed.This is despite delay to early endoscopy on weekends,a large proportion of hospitals without out of hours endoscopy services, and other likely organisational factors on weekends including reduced staffing patterns of physicians,nurses and other support staff.

113

Psychological Influences and Central Mechanisms in Pathogenesis of FV

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Objective To explore the features of brain activity in Functional vomiting (FV) patients and to elucidate the possible central mechanisms. Methods 8 healthy subjects (HS) (F, age 28.0±5.2) and 8 FV patients (F, age 27.8±6.8) participated in this study. Both HS and FV patients completed questionnaires including Zung self-rating anxiety and depression scale (SAS/SDS) and Eysenck personality questionnaire (EPQ). Cutaneous electrogastrography (EGG), gastric empting (GE) of radiopaque markers, perfusion nutrition load test (PNLT) and intragastric pressure (IGP) were performed in patients. Using the regional homogeneity (ReHo) approach, we compare the brain activity between the 2 groups and examine the relationship between gastric function and brain activity in FV patients. Results FV patients had significant anxiety/depression states and neurotic personality (SAS P=0.002,SDS P= 0.001,EPQ-N P=0.005). Compared with healthy controls, increased ReHo was found in FV patients in many limbic areas including the bilateral mid-cingulate cortex (MCC, BA 24 and 32), left amygdala, right insula cortex, right thalamus, and other areas as left caudate nuclei, bilateral frontal sensory and motor areas (BA 5 and 6). Decreased ReHo was found in the bilateral occipital lobe (BA 18 and 19), bilateral orbitofrontal cortex (BA 11) and right middle temporal gyrus (BA 39). Postprandial dominant frequency of EGG was negatively correlated with ReHo in the bilateral MCC, left middle frontal gyrus, and was positively correlated with ReHo in the bilateral cuneus and right middle temporal gyrus. Conclusion Our findings indicated that abnormal brain activity was distributed in limbic areas predominantly in FV patients during resting state. Some peripheral disturbances of gastric function might be related to specific abnormal patterns of brain activity. Abnormalities of cognition-emotion, visceral sensory and motor functions could contribute to the pathogenesis of FV together.

114

Altered Expression of *Ano1* Variants in Gastroparesis

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Background: *Ano1* is a recently identified Ca^{2+} activated Cl^- channel expressed in interstitial cells of Cajal (ICC). Several transcripts of *Ano1* are generated by alternative splice sites. The alternative sequences code for protein segments previously named *b* (exon 6b), *c* (exon 13) and *d* (exon 15).The *a* segment results from use of an alternative transcriptional start site. Previous studies have shown that alternative splicing may be organ-specific and contribute to altered channel properties. Isoforms *b* and *c* influence the Ca^{2+}-sensitivity and voltage-dependence of *Ano1*, respectively. ICC loss has been described in gastroparesis but the pathophysiology of this disease is not well understood. Aim: Determine the expression of *Ano1* transcript variants in gastric muscularis propria of patients with gastroparesis. Methods: Full thickness biopsies were collected from the gastric body of 16 patients with diabetic (DG, n=8) and idiopathic (IG, n=8) gastroparesis. Age- and sex-matched controls were obtained from patients undergoing surgery for obesity. Quantitative RT-PCR was carried out to evaluate the relative abundance of *Ano1* splice variants in control and gastroparetic tissues. Results: Expression of the 4 spliced segments was quantified using total *Ano1* (i.e., a sequence common to all isoforms) as reference (see Table). The DG group had significantly lower levels of *a* and *d* and significantly higher levels of *b* compared to the control group whereas The IG group had significantly lower levels of *d*. Expression of segment c did not vary between groups. Conclusions: Expression of *Ano1* variants in gastroparesis patients differs from controls. The higher expression of the *b* segment raises the possibility that *Ano1* channels in diabetic patients with gastroparesis have reduced calcium sensitivity compared to *Ano1* in normal controls. Further studies are needed to explore the significance of this finding as well as to determine the role of *a* and *d* segments in the regulation the *Ano1* channel and gastric motility. Supported by NIH grant DK57061, DK73983 and DK74008 (the Gastroparesis Clinical Research Consortium, GpCRC).

	a	*b*	*d*
Control	0.195, 0.14-0.22	0.18, 0.12-0.2	0.97, 0.7-1.5
DG	0.1, 0.08-0.14*	0.29, 0.22-0.44*	0.48, 0.3-0.68*
IG	0.11, 0.03-0.19	0.17, 0.12-0.4	0.43, 0.14-0.62*

Data are median, IQR. *p<0.05 Kruskal-Wallis ANOVA on ranks with Dunn's multiple comparisons post-test.

115

Upregulation of Dopamine Receptor 2 Expression in Gastric Neurons and Interstitial Cell of Cajal in Diabetic Rats Contribute to Tachygastria Evoked by Hyperglycemia

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Up to 75% of diabetic gastroparesis patients may experience gastric tachygastria leading to persistent nausea and vomiting. Domperidone, a dopamine 2 receptor (D2) antagonist has been used clinically to treat diabetic tachygastria. However the mechanism by which dopamine contributes to diabetic tachygastria is not clear. We hypothesize that hyperglycemia via dopamine pathway inhibits pacemaker activities in the gastric corpus but stimulates ectopic electrical activities in the antrum and this is mediated by differentiation activation of D2 receptors of the interstitial cell of Cajal in these two different regions of the stomach. To test this hypothesis we performed mapping of gastric electrical activities using Teflon coated wires anchored to the gastric corpus and antrum. Glucose clamping at 350±50 mg/dl resulted in gastric dysrhythmias. It caused a marked reduction in the power of dominant frequency (5 cpm) of the corpus and produced tachygastria with a 3-fold increase in the power of the frequency of the antrum. These effects were blocked by domperidone (0.4 mg/kg). The dysrhythmic effects of hyperglycemia were reproduced by dopamine (0.2 mg/kg iv) showing an inhibiting action in the corpus but a stimulating effect in the antrum. Western blots analysis showed that D2 receptor expression in the gastric antrum is 50% more than in the corpus (P<0.05). Immunohistochemistry demonstrated an abundance of D2 receptors in the gastric neurons containing NOS and ChAT. All ICC also contained D2 receptors. In 4 wk streptozotocin-induced diabetic rats, D2 receptor gene and protein expression in the gastric tissue were increased by 60% and 39% compared to age-matched controls (P<0.05). Glucose infusion (20% dextrose, 10 μl/min) provoked gastric dysrhythmias in this group of diabetic rats and these were prevented by domperidone (0.4 mg/kg). Domperidone also reversed PGE-2 induced tachygastria in the antrum suggesting that dopamine is acting downstream of the prostaglandin pathway. In conclusion, both hyperglycemia and dopamine inhibits native pacemaker activities in the corpus and activates ectopic electrical activities in the antrum. These are mediated by D2 receptors in the ICC and gastric neurons which are upregulated in diabetes. The dopaminergic pathway acts downstream of PG. Blockade of D2 receptor is highly effective to prevent tachygastria stimulated by PG, dopamine and hyperglycemia. The upregulation of D2 receptors in the ICC and gastric neurons in diabetes may contribute to the propensity for diabetics to develop tachygastria. It also provides a rationale for using D2 receptor antagonists in the treatment of this condition.

116

Mental Stress Increases Meal-Induced Symptoms Severity by Sympathetic Hyperactivity and Enhanced Endocrine Response in Patients With Postprandial Distress Syndrome

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Background and Aim: Previous data show that psychological stress may alter gastric sensory-motor function. Neuro-hormonal mechanisms underlying this phenomenon in dyspeptic patients remain to be clarified. Aim of the present study is to assess autonomic nervous system activity and hypothalamic-pituitary-adrenal (HPA) axis hormones in response to mental stress before and after meal in dyspeptic patients. Subjects and methods: Fifteen patients with postprandial distress syndrome (PDS) (8 M, 21-40 years) and eight healthy controls (4 M, 19-28 years) underwent electrogastrography (EGG) and gastric emptying study (13C-octanoic acid breath test) using a 480 Kcal solid meal. Heart rate variability assessment (LF/HF ratio) by ECG and CRF, ACTH and cortisol on serum samples collected every 30 minutes for 5 hours were also evaluated. Dyspeptic symptoms (postprandial fullness and early satiety) were scored at same time points by analogue visual scale and expressed as sum of total symptoms scores (TSS). The study protocol, with and without a standardized

mental stress (MS) test (serial numeric calculations for ten minutes) before the meal, was repeated in a random order in two different days. Results: Dyspeptic symptoms were present only in patients and were exclusively meal-related. In patients, but not in controls, MS significantly increased symptoms severity (TSS: 738±635 vs 288±301, p<0.05). LF/HF ratio was significantly higher in patients during postprandial period with than without MS (5.38±3.48 vs 2.78±0.92; p<0.05), whereas in controls it remained unmodified. In addition, a significant increase of ACTH postprandial levels after MS in patients (stress 6.63±3.11 pg/ml vs no-stress 3.72±2.07; p<0.05) was found, while in controls no modifications were observed. CRF and cortisol were unmodified both in patients and controls. Gastric emptying rate was delayed in 60 % of patients, but it was not influenced by MS. EGG did not show any modification. Conclusions: In PDS patients, concurrent administration of mental stress and meal increases symptoms severity by inducing enhanced sympathetic activity and increased HPA endocrine output. As the gastric emptying looks not altered, we can assume that these neuro-hormonal responses mainly affect gastric sensitive function.

117

Inhibition of CaMKII Prevents Nitrergic Neuropathy in Gastric Myenteric Plexus in Diabetic Rats

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Selective damage to gastric nitric oxide (NO)-containing neurons occurs in diabetes and results in defective accommodation and gastroparesis. Previously we demonstrated that upregulation of NR2B receptors occurrs in diabetes and that chronic activation of NMDA receptors may be harmful to gastric NOS neurons. Calcium influx through NMDA receptor stimulates Ca^{2+}/calmodulin-dependent protein kinase type II (CaMKII), an enzyme which interacts with NR2B subunit. This is key for induction of synaptic plasticity. We hypothesize that CaMKII is critical to NMDA-mediated nitrergic neuronal degeneration in the stomach. Inhibition of the activities of CaMKII may prevent nitrergic cell death. To test the hypothesis, we performed studies in 8 wks streptozotocin (STZ)-induced diabetic rats. Protein analysis showed that NMDA receptors in the cell membrane fractions of diabetic gastric tissue was 1.3 fold increase compared to the control group, suggesting an upregulation of NMDA receptors in diabetes. Further analysis demonstrated that NR2B and pCaMK II was increased by 67 % and 30%, respectively, in the diabetic group and these two molecules colocalized in the PSD fractons. Immunohistochemical staining showed that gastric NOS neurons which contained NMDA receptor subunits NR2B also stained positive for pCaMKII. To determine whether nitrergic neuronal degeneration in diabetes is mediated by upregulation of pCaMKII, we performed *In Vivo* studies in STZ-induced diabetic rats. 2 wks after induction of diabetes by STZ, rats were treated with a CaMKII inhibitor, KN-93 (1mg/kg, i.p.) every other day for 6 wks. Compared to control, KN-93 treatment caused a 55% decrease in pCaMKII protein expression. This was accompanied by a 75% decrease in the expression of active caspase-3 (a marker of apoptosis) and prevention of nitrergic neuronal loss. In a separate study, electroporation of CaMKII siRNA was performed on the gastric wall in 2-wk diabetic rats. 3 wks after electroporation, there was a decrease in CaMKII and active caspase-3 by 64% and 45%, respectively. It also reduced the loss of NOS protein from 72% to 25%. In conclusion, we showed that upregulation of NR2B receptors and pCaMKII occurred in diabetes. Activation of the NR2B receptor subunits by pCaMKII may play an important role in the induction of selective nitrergic neuropathy in diabetes, as this event could be prevented by inhibition of CaMKII. This may prove to be a novel approach in reducing diabetic neuronal degeneration in the stomach.

118

Increased Expression of M2c Macrophage-Associated Gene Transcripts in Diabetic Mice Resistant to Delayed Gastric Emptying

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Background: Gastroparesis is a well recognized complication of diabetes. In the NOD mouse, onset of diabetes (DM) is associated with up-regulation in the gastric muscularis propria of heme oxygenase-1 (HO1) and a switch from conventionally activated M1 macrophages to alternatively activated, CD206+ M2 macrophages (AAMs). Mice that develop delayed gastric emptying (GE) have fewer M2 macrophages and reduced HO1 expression. M2 macrophage subpopulations (M2a, M2b and M2c) are reported to be heterogeneous in their expression of cytokines and enzymes involved in nitric oxide (NO) and heme metabolism. The aims of this study were to determine if mRNA for proteins associated with different types of macrophages change during development of delayed GE. Methods: RNA was extracted from full-thickness gastric body tissues from NOD mice using RecoverAll™ (Ambion). Real-time PCR was carried out using RT^2SYBR®Green/ROX™ qPCR master mix. Data were normalized to expression of GAPDH, a housekeeping gene. mRNA levels for arginase (decreases NO generation), inducible nitric oxide synthase (iNOS, increases NO), interleukin-10 (IL-10, induces HO1), and CD163 (heme transporter) were measured. 4 groups (each n=4) of mice were studied: non-DM controls, DM mice with delayed GE and mice with 2 or 10 weeks of DM but normal GE. The 10-wk DM group is considered resistant to the development of delayed GE. The data were analyzed using the $\Delta\Delta$Ct method and expressed as fold change relative to levels in non-DM mice. Results: Significant differences in the expression of the transcripts were detected between the 4 groups (see Table). DM mice resistant to development of delayed GE (10 wk DM) had the highest levels of IL-10. Arginase levels were highest during early DM and declined with time. Mice with delayed GE had the highest levels of iNOS and low levels of IL-10 and arginase. Conclusion: During early DM, high arginase levels indicate expression of the M2a subtype of AAMs. In DM mice resistant to delayed GE, high levels of IL-10 indicate expression of the M2c subtype. In mice with delayed GE, markers of M2 macrophages were very low. Regulation of macrophage phenotype may therefore offer an additional therapeutic option for diabetic gastroparesis. Supported by NIH grants DK68055 and DK57061.

	GE	iNOS	Arginase	IL-10	CD163
2 wk DM	Normal	23.2, 20.2-33.5	*31.2, 28.1-35.1	3.0, 2.0-4.1	1.0, 0.8-1.1
10 wk DM	Normal	0.7, 0.2-1.2	4.7, 3.7-6.0	*15.2, 13.7-17.1	5.0, 4.2-7.0
5.5 wk DM	Delayed	*56.0, 45.1-79.0	1.2, 1.0-1.4	0.4, 0.2-0.7	1.0, 0.8-1.1

Changes reported as medians, IQR. * $p < 0.05$ by Kruskal Wallis ANOVA on ranks with Dunn's multiple comparisons post test

119

European Phylogenetic Origin of *Helicobacter pylori* Strains as a Risk Factor for Premalignant Gastric Lesions in Colombia

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Background: The prevalence of *Helicobacter pylori* (Hp) is uniformly high in Colombia. In Narino, individuals living in the mountains have a 25-fold greater risk (high risk, HR) for developing gastric cancer than those living on the Pacific coast (low risk, LR). While the virulence gene *cagA* and the *vacA s1m1* allele are linked to gastric cancer risk, the importance of the phylogeny of Hp strains has not been studied. Our aim was to define the relationship between phylogenetic characteristics of clinical Hp isolates and premalignant gastric lesions in Colombia. **Methods:** Gastric biopsies were taken from 89 men (ages 40 - 59) with dyspeptic symptoms and Hp strains were isolated from 81 subjects. Of these, 63 strains were genotyped as *cagA*+ and *vacA s1m1*. We randomly selected 20 of these strains from each of the LR and HR regions (40 strains total). Phylogenetic analysis was performed by multilocus sequence typing (MLST) based on 7 housekeeping genes (*atpA*, *efp*, *mutY*, *ppa*, *trpC*, *ureI*, and *yphC*). Allelic profiles were compared to >400 reference strains. The phylogenetic tree was constructed using the Neighbor joining method and 10,000 bootstrap replicates. Histopathologic categories were: 1, normal; 2, non-atrophic gastritis; 3, multifocal atrophic gastritis; 4, intestinal metaplasia; 5: dysplasia; extent and severity were quantified in categories 3 - 5. **Results:** By MLST analysis 20/20 (100%) of strains isolated from HR subjects exhibited genotypic characteristics of European isolates (hpEurope), whereas 12/20 (60%) of the LR strains clustered with African strains (10 hpWAfrica and 2 hspSAfrica) and the remaining 8/20 (40%) LR isolates clustered as European ($p < 0.0001$ HR vs. LR). Analysis of histopathological scores indicated that subjects infected with hpEurope strains had more advanced lesions than those infected with hpAfrican strains ($p < 0.05$; Table). While tissues from HR subjects showed a trend toward higher lesion scores than the LR cases, this difference was not significant (Table). **Conclusions:** Hp strains from subjects in the HR region exhibited only European ancestry, while in the LR region, European and African strains were represented. Strain phylogenetic origin was a strong predictor of histopathology, and Hp strains of European origin are associated with more advanced gastric lesions.

	n	Histopathology Score (1 - 5)
hpEurope	28	3.85 ± 0.18^a
hpWAfrica + hspSAfrica	12	3.13 ± 0.35
High Risk region (HR)	20	3.90 ± 0.20^b
Low Risk region (LR)	20	3.37 ± 0.27

[a]$p = 0.0483$ for European vs. African strains; [b]$p = 0.1010$ for HR vs. LR.

120

Coronary Artery *in Situ Helicobacter pylori* and Its Association With Stress and Atherosclerosis in Monkeys

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Background. Coronary atherosclerosis is associated with high dietary fat/cholesterol, chronic stress, and systemic inflammation. Presence of inflammation in coronary atheromas suggests a role for bacteria and CagA+ *H. pylori* has been observed within atherosclerotic plaques. **Aims and Design.** To determine the role of *H. pylori* in coronary artery atherogenesis in a naturally *H. pylori* infected primate model, 75 wild caught Cynomolgus monkeys enrolled in a dietary soy intervention study were evaluated for *H. pylori*, social status as a measure of psychosocial stress, and coronary artery plaque size and inflammation. Necropsy was performed at six years and the first 5mm of the left circumflex coronary artery from each animal was serially sectioned for determination of intimal area (mm^2) and maximum intimal thickness (mm) by histomorphometry, intraplaque macrophage and T cell content by immunohistochemistry, and *H. pylori* density via *16S rRNA* and *cagA* fluorescence *in situ* hybridization. Stomach sections were also evaluated for *H. pylori 16S rRNA* and *cagA* expression. **Results.** *H. pylori 16S rRNA* was present in the stomach and coronary artery of 56% and 42% of the monkeys, respectively, and there was a strong positive correlation between gastric and arterial infection (r=0.87, p<0.0001). Subordinate animals were at greater risk for infection (*16S rRNA*: OR 4.53, CI 1.621-12.643, p=0.004; *cagA*: OR 2.95, CI 1.059-8.195, p=0.04). Dietary soy intervention had no significant effect on *H. pylori* prevalence in either the coronary artery or stomach. Maximum intimal thickness was greater in arteries expressing *16S rRNA* [0.26mm (CI 0.19-0.34) vs 0.17mm (CI 0.12-0.22), p=0.04] and *cagA* [0.27mm (CI 0.20-0.36) vs 0.17mm (CI 0.13-0.22), p=0.02], and intimal area tended to be greater in those arteries but did not reach statistical significance. *H. pylori* positive arteries were more likely to contain macrophages (*16S rRNA*: OR 3.76, CI 1.148-12.292, p=0.03; *cagA*: OR 3.60, CI 1.156-11.189, p=0.03), but prevalence of T cells did not differ. **Conclusions**. The strong correlation between gastric and arterial *H. pylori* infection, coupled with the association between *H. pylori* and larger, more inflamed plaques, suggests that this organism is playing a role in atherogenesis. This observation is supported by the significantly