recipient or a donor/recipient mismatch (MMP-2: 57.8% and MMP-9: 33.9%) and chimerism were not associated with the development of late phase I/R injury or rejection in the OLT patients, although serological differences in the MMP levels, e.g. rejection-related MMP-9 peak levels 1 week after OLT, did occur. In conclusion: MMP-2 and MMP-9 gene promoter polymorphisms and donor/recipient mismatches do not seem to contribute to late phase I/R injury or rejection after liver transplantation. Serological changes in the MMP-2 and MMP-9 levels occur independent of the MMP genotype in liver disease patients and after liver transplantation.

S1803

***In Vitro* Hepatocyte Differentiation of Mesenchymal Stem Cells Derived from Human Bone Marrow**

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Introduction : In addition to long-term self-renewal capacity, human mesenchymal stem cells(MSCs) possess versatile differentiation potential ranging from mesenchyme-related multipotency to neuroectodermal and endodermal competency. Of particular concern is hepatogenic potential that can be used for liver-directed stem cell therapy and transplantation. In this study examined whether human bone marrow-derived MSCs are able to differentiate into hepatocytes. Materials and methods : MSCs were cultured 2-step protocol with use of hepatocyte growth factor and oncostatin M. In the course of cell differentiation, cell morphology was observed by LM, EM and PLD activity and the expression of ALB, AFP, CK-18, CK-19, CPS, GS and GAPDH of heaptocyte were confirmed by Western blot analysis and RT-PCR. Hepatocyte functional activity were confirmed by glycogen storage and uptake of low-density lipoprotein(LDL). Results : After 3 weeks of induction, cuboidal morphology, which is characteristic of hepatocytes, was observed, and also cell expressed marker protein specific of liver cell such as albumin, CK 18, and PEPCK. The presence of stored glycogen, as determined by PAS staining, was visualized at 4 weeks differentiation. After 6 weeks of differentiation, hepatocytes demonstrated the ability to uptake significant levels of LDL. Early phase of differentiation, we observed morphologic change and cell organelles including Golgi body, mitochondria and ER by EM. Also PLD activity in the hepatic differentiation cells increased twofold or more at the 30 min point. Conclusions : MSCs from human bone marrow could differentiate into hepatocyte or hepatocyte-like cells in the differentiation media including HGF, FGF, EGF and OSM. Based on these observation, we conclude that human MSCs retain hepatogenic potential suitable for cell therapy and transplantation against intractable liver diseases.

S1804

Altered Kynurenine Pathway Metabolism in Irritable Bowel Syndrome (IBS)-Evidence of Indoleamine 2,3-Dioxygenase (IDO) Activation in a Male Cohort

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Background: IBS is a common disorder of the gastrointestinal tract (GIT) which affects 10-15% of the population. Although the pathophysiology remains unclear, it is increasingly being viewed as a disorder of the brain-gut axis. In particular, accumulating evidence points to the involvement of both the central and peripheral serotonergic systems in disease symptomatology. Serotonin is involved in regulating GIT secretion, motility and perception and its central role in the regulation of mood are also well documented. Low level immune activation has also been implicated in the IBS. The kynurenine pathway of tryptophan degradation may serve to integrate these findings. Aim: To investigate tryptophan degradation along this pathway in a male IBS cohort. **Methods:** We studied 10 male IBS patients and 26 gender-matched controls. Trytophan and it's metabolites were measured by HPLC in a single isocratic run using sequential fluorescent and UV detection. Neopterin, a sensitive marker of immune activation, was measured using a commercially available ELISA assay. **Results:** Both kynurenine levels (656.8 ± 60.1 vs 530.7 ± 24.3 ng/ml, p<0.05) and the kynurenine:tryptophan ratio (0.0605 ± 0.0045 vs 0.0494 ± 0.0017, p < 0.01) were significantly increased in our IBS cohort. Neopterin levels (8.41 ± 1.08 vs 4.25 ± 0.29 nmol/L , p < 0.0001) were also increased in the IBS subjects and the levels of the neuroprotective agent kynurenic acid were decreased (3.23 ± 0.336 vs 6.75 ± 0.557 ng/ml) as was the kynurenic acid:kynurenine ratio (0.0059 ± 0.0006 vs 0.0126 ± 0.0007,p < 0.001).**Summary:** These findings suggest that the activity of indoleamine-2,3-dioxygenase (IDO), the immunoresponsive enzyme which is responsible for the degradation of tryptophan along this pathway, is enhanced in IBS patients relative to controls. This provides novel evidence for an immune-mediated degradation of tryptophan in a male IBS population and may point to new therapeutic avenues in this debilitating condition.

S1805

Dietary Lectins As the Environmental "Unknown Pathogen" in Parkinson's Disease

Jolene Zheng

Idiopathic Parkinson's disease (PD) is a late-onset (50-60 yr), chronic and progressive motor dysfunction due to loss of dopamine (DA) neurons, caused by presence of aggregated α-synuclein (α-SYN) and Lewy's bodies (LB). Nigrostriatal DA neurons appear to be targeted preferentially because of their high concentration of neuromelanin that facilitates α-SYN inclusions. In animal models, overexpression or mutations of α-SYN induce the LB, DA deficits and parkinsonism. Genetic mutations, however, are not the sole trigger of PD. Braak's group has hypothesized that an "unknown pathogen" penetrates the gastrointestinal (GI) wall and enters the CNS via retrograde transport through the vagus nerve. This "unknown pathogen" induces gradual onset CNS degeneration in ascending order from the dorsal motor nucleus of the vagus (DMV) to higher neuronal structures. PD patients have major GI dysfunctions and swallowing impair. Brainstem DMV catecholaminergic neurons have recently been implicated in the control of esophago-gastric reflexes and DA has profound effects on gastric projecting DMV neurons. Epidemiology linking diet and PD has shown that higher prevalence of PD is observed from vegetarians vs. a diet dominated by meat consumption. Dietary phytochemical lectins are present in vegetables/seeds. The aim of this study was to test the hypothesis that dietary lectins are transported to the dosal vagal complex where they induce α-SYN aggregation. Using a rat model we have observed that incubation with lectin (300 nM), wild-type α-SYN (10μM) and Bodipy Maleimide conjugated α-SYN (10nM) induces α-SYN aggregation which was avoid when lectin was omitted from the solution; FITC labeled cells are present in the brainstem of animals fed with 0.1% FITC-lectin (300μl per os/day x3), whereas rats fed with vehicle or fluorescent tracer DiI did not show fluorescence in the CNS; and whole cell patchclamp recordings in thin brainstem slice showed that neuromelanin (100nM) excites a subgroup of gastric-projecting DMV neurons, indicating that DMV neurons express neuromelanin receptors on the membrane. Our data suggest that lectins are able to induce neuronal α-SYN aggregation and, possibly, the inclusion of LB. Dietary phytochemical lectins are indeed transferred and transported retrogradely from the GI tract to the CNS. Lectins, by virtue of their permeability, could also act as a chaperon for viruses and toxin(s), including those that may be responsible for α-SYN inclusions in PD. It must be kept in mind, though, that the lectin-mediated insult (if any) is gradual and might be determined by the association of lectins with other food structures. Supported by NIDDK # 1P30 DK072476

S1806

Central Neuronal Mechanisms of GES and Effects of Stimulation Parameters and Locations in Regular and Diet-Induced Obese Rats

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Gastric electrical stimulation has been used for the treatment of obesity with unclear central mechanisms. The purposes of this study were to compare the difference in neuronal responses of the ventromedial hypothalamus (VMH) to GES between regular rats and diet-induced obese (DIO) rats and to optimize stimulation parameters and locations. Methods: Spontaneous unit discharges of 83 neurons in the VMH were recorded from 22 rats: 10 regular rats and 12 DIO rats. Gastric distention (GD) with 20 and 40 or 60mmHg was performed to determine whether the neuron was responsive to GD of low or high threshold. After a neuron of the VMH was identified as a GD-responsive neuron, GES with different stimulation frequencies (10, 20, 40 and 100Hz), pulse widths (0.1, 0.3, 0.6, 1.2 and 3ms), train-on times (0.1, 0.5, 1 and 2s) and amplitude (3, 6 and 10mA) was applied. VMH neuronal responses to GES at three different locations (distal antrum/A, middle greater curvature/M and proximal greater curvature/GC) were also tested. Results: 1) The DIO rats were more resistant to GD and GES than the regular rats. A significantly lower percentage of neurons (12/38, 31.6%) were activated by gastric distention of 20mmHg in the DIO rats, compared with that in the regular rats (14/23). Similarly, the percentage of responses to GES of 0.3ms in the DIO rats was significantly lower compared with that in the regular rats (P<0.03). 2) Different stimulation parameters resulted in different neuronal responses. For the stimulation frequency, there was an increase in neuronal responses from 10Hz to 40Hz (10Hz vs. 40Hz, p<=0.001). However, GES of 100Hz did not yield a higher response rate than GES of 40Hz. For the pulse width, the neuronal response rate was proportional to the pulse width up to 3ms (0.1ms/3ms, p<=0.001; 0.3ms/3ms, p=0.033; 0.6ms/3ms, p=0.020); Similar findings were noted with the train on-time (0.1s/2s, p<=0.001; 0.5s/2s, p=0.045). For pulse amplitude, 6mA seemed to be sufficient (3mA/6mA, p=0.029; 6mA/10mA, p=0.889). GES of these parameters activated a vast majority (84%) of the tested neurons. 3) GES at distal antrum activated a higher percentage of neurons than GES at other locations (A/GC, p=0.008). Conclusion: DIO rats are significantly less responsive to physiological gastric distention as well as gastric electrical stimulation. Based on the neuronal responses in the VMH, the best stimulation parameters for GES are as follows: train on-time of 2s, off-time of 3s, pulse frequency of 40Hz, width of 3ms (or higher) and amplitude of 6mA. The best stimulation location seems to be the distal antrum. (The work was supported by Medtronic Inc).

S1807

Cognitive Coping Mechanism of Limbic/Paralimbic System in the Modulation of Placebo Analgesia in Visceral Pain: A 3t-fMRI Study

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Background Visceral pain is the cardinal symptom of functional GI disorder (FGID). Visceral sensation is also described as more unpleasant than somatic sensation, suggestive of higher cognitive/affective components in visceral pain. Current treatment for FGID is unsatisfactory and associated with high placebo response. The central mechanism responsible for the placebo effect in visceral pain is unclear. **Aim** To test the hypothesis that the placebo response to visceral pain is associated with the cognitive/affective regions in brain. **Method** 13 right-handed subjects (9F; 24.1±3.9 yrs) received brain fMRI in evaluating visceral pain evoked by 'moderate' painful esophageal balloon distention (22.7 ± 4.7 mmHg). Each subject received placebo and control session using block design in random order. In placebo session, the subjects were told that a newly developed short-acting 'pain killer' (5 ml saline IV) would be given before the painful distension. While in control session, the subjects were told that the same amount of saline would be given as a control. Pain catastrophization scale (PCS) was obtained from every subject before the task. Visual analogue scale (VAS) and short form McGill pain questionnaire were enquired after each session. Regression analysis to directly delineate a correlation map of the placebo effect between the differences of neuronal activation and psychophysical measurement (control-placebo) across individuals was obtained using SPM5. **Results** (1) The VAS score and McGill total pain rating index were significantly lower during the placebo than the control sessions (P<0.05). (2) Esophageal pain in both placebo and control session activated a wide range of cortical and subcortical network, including, S1/S2, insula, thalamus, anterior and posterior cingulate cortices, superior temporal gyrus, midbrain, and prefrontal cortex. However, the numbers of the activated voxels were significantly reduced during the placebo sessions (P<0.01). (3) PCS scores showed an inverse relationship with intensity of placebo effect (r=-0.609, P=0.04), which suggests the thoughts toward pain may influence the placebo effect. With regression analysis, anterior cigulate

(BA24), prefrontal (BA9,10,46), and superior temporal gyrus (BA22) were the regions positively correlated to the placebo effect measured by VAS or McGill pain rating index. **Conclusions** (1) Significant reduction in pain and brain activation within pain related regions occurred during the placebo analgesia in visceral pain. (2) The correlation between the activation differences in limbic/paralimbic region and placebo intensity may suggest a cognitive coping mechanism in modulating placebo analgesia.

S1808

Exploring the Neural Processing of Visceral Sensations: the Influence of Sensory, Emotional and Cognitive Factors

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INTRODUCTION: Aetiology of Functional Gastrointestinal Disorders may be a result of aberrant brain processing of visceral sensation due to psychological disturbances. Through a series of studies, we have used functional magnetic resonance imaging (fMRI) to assess the influence of psychological factors on the brain processing of oesophageal pain in healthy volunteers. METHODS: Study 1) 7 healthy volunteers (6 male, age range 20-25 years) underwent four separate fMRI scans incorporating four levels of phasic oesophageal stimulation (OS) ranging from non-painful to painful. Study 2) Whilst performing a distraction task, 12 healthy volunteers (all male, age range 21-32 years) underwent four separate fMRI scans incorporating four levels of phasic OS ranging from non-painful to painful. In addition, a fifth scan was performed during painful OS without distraction. Study 3) 12 healthy volunteers (all male, age range 21-32 years) fMRI images were acquired during two experimental runs in which volunteers received phasic painful OS under negative and neutral mood induction. RESULTS: Study 1) Mean VAS scores increased progressively with increasing OS intensity (χ^2 = 10.9, df 3, P=0.001). Bilateral activity in the anterior cingulate cortex (ACC) and primary somatosensory cortex (SI) was correlated with level and perceived intensity of OS ($p<0.05$, Bonferroni corrected). Study 2) Bilateral SI and left ACC activity increased with level of OS. Focusing attention on pain increased pain ratings and intensity of activity in the right ACC, and right frontal cortex ($p<0.05$, corrected for multiple comparisons). Study 3) During negative mood induction, OS was associated with an increase (compared to neutral mood) in brain activity in the right anterior insula and right ACC ($p<0.05$, corrected for multiple comparisons). CONCLUSIONS: Bilateral SI and left ACC appear to encode sensory aspects of OS such as intensity. Activity in the right ACC is altered by attention, and both right insula and right ACC are modulated by negative mood induction suggesting involvement of these regions in cognitive and emotional components of pain processing. Evidence of right hemispheric dominance during emotional and cognitive manipulation supports the view the right hemisphere is predominately associated with sympathetic activity (arousal, negative affect) and that the right insula and right ACC are integral for subjective awareness of emotion. These studies provide new insights into complex interactions that comprise the visceral pain neuromatrix which may be important in future experiments applied to studying functional clinical disorders that have pain as a primary symptom.

S1809

Repeated Esophageal Distension Shortens the Stimulus Response Latency of fMRI Activation Signals

Mark Kern, Adeyemi Lawal, Reza Shaker

Balloon distension is traditionally used for the study of upper and lower GI sensory function. The effect of repeated periodic balloon distensions on fMRI signal timing characteristics has not been systematically studied. This information is crucial when analyzing fMRI signals using general linear model or correlation statistical techniques. Aims: 1) To determine the latency between the onset of proximal esophageal distension and the peak of fMRI signal change associated with that distension. 2) Compare the latencies for three consecutive esophageal distensions within and between subjects. Methods: We studied 12 healthy adult subjects (age: 18-35) during fMRI scanning of the insula (n=6) or cingulate gyrus (n=6) (eleven 2.5 mm thick sagittal slices, 96x96 pixel within slice resolution, 24 cm FOV). Paradigm-driven, 2-minute fMRI scans were performed during alternating intervals of randomly timed rest and 15-second intervals of barostatically controlled esophageal distensions. Separate scans with perceived and subliminal esophageal distension pressures were performed. A general linear model was utilized to identify fMRI time-series that varied significantly with proximal esophageal distension. These activation time-series were partitioned into three epochs designated stimulation 1, 2 and 3 and the latency from the onset of distension to the peak of fMRI signal intensity was measured. Within cortical sub-regions, latencies were compared between stimulation epochs for subliminal and liminal esophageal distension as well as between subliminal and liminal stimulation for each epoch. Results: Significant differences were found among the latency values of fMRI signal changes associated with both subliminal and liminal proximal esophageal distensions when comparing consecutive, repeated distensions (Table). As seen, the latency for the third stimulation (stim3) was significantly shorter (*$p<0.05$, corrected, RMANOVA) than the stim1 and stim2 latencies for the anterior cingulate (AC), posterior cingulate (PC) and anterior insula (AI) but not the posterior insula (PI). PI showed significant differences only for perceived distensions. Conclusions: Repeated identical distensions significantly shorten the stimulus-onset to peak fMRI activity latencies in the proximal esophagus. This finding must be taken into account when modeling signal characteristics for the general linear model, regression and correlation analysis protocols utilized in detecting fMRI signal changes associated with visceral mechanical stimulation.

Latency in seconds	AC			PC			AI			PI		
	Stim1	*Stim2*	*Stim3*	*Stim1*	*Stim2*	*Stim3*	*Stim1*	*Stim2*	*Stim3*	*Stim1*	*Stim2*	*Stim3*
liminal	20±11	19±10	12±8*	18±10	19±10	13±10*	17±10	18±11	13±8*	17±10	18±8	11±10*
subliminal	19±13	22±13	14±10*	19±11	19±10	12±8*	23±10	16±11	11±7*	17±10	13±8	8±7

S1810

Evaluation of Spino-Anorectal Pathways in Spinal Cord Injury with Bowel Dysfunction Using Magnetic Stimulation: A Novel and Noninvasive Test

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INTRODUCTION: Spinal cord and cauda equina injury can cause distressing symptoms and pelvic floor dysfunction. Currently, there is no specific test for evaluating these problems as well as spino-anorectal pathways. Pudendal nerve latency (PNTML) provides limited and conflicting data. AIM: We tested the hypothesis that motor evoked potentials (MEP) of anorectum using translumbar and transsacral magnetic stimulation provides comprehensive pathophysiologic information regarding spino-anorectal pathways in patients with spinal cord injury when compared to PNTML. METHODS: 22 (M/F 9/13) patients with history (median duration=3 yrs) of spinal cord injury (cervical-2, thoracic-2, lumbosacral-14, multilevel -4), mean age 49±16 yrs and 11 healthy subjects were assessed. Magnetic stimulations were performed with a Cadwell Focalpoint Coil™ (9-cm) placed over the right and left of midline at L3-L4 and S1-S3 levels using 80-100% intensity. Anal and rectal MEPs were measured after lumbar and sacral stimulations by placing a novel probe containing 2 pairs of bipolar steel ring electrodes, located in the rectum and anal canal. PNTML (St. Mark's electrode) and MEP latencies were compared and their clinical utility was assessed. RESULTS: MEPs were significantly prolonged on both sides and in the lumbar and sacral regions in patients compared to controls (Table= mean ± 95% CI). Abnormal MEPs were detected in 16 (80%),13 (65%), 14 (70%), and 11 (55%) patients respectively in the lumbo-anal (TL-aMEP), lumbo-rectal (TL-rMEP), sacro-anal (TS-aMEP), and sacro-rectal (TS-rMEP) tracts. A single abnormal MEP was identified in 20 (100%) patients and abnormal PNTML in 13 (65%) patients (p= 0.05). Abnormal MEP was detected on right side in 19 (95%) and left side in 20(100%) and abnormal PNTML in 13(65%) patients on each side. MEPs and PNTML were unobtainable in 2 patients each from technical problems. CONCLUSIONS: Translumbar and transsacral MEPs provide clear delineation of the spino-rectal and spino-anal pathways and reveal significant neuropathy in spinal cord injury patients. It is a superior test to PNTML. The test is well tolerated and offers a safe, inexpensive, and objective method of evaluating peripheral brain-gut pathways and hitherto unknown information regarding pelvic floor neuropathy and enhance diagnostic yield.

	Left(milliseconds)			Right(milliseconds)		
	Control	Patients	*p*-value	Control	Patients	*p*-value
TL-aMEP	3.2 ± 1.1	7.1 ± 1.3	0.00001	3.0 ± 1.1	7.5 ± 2.1	0.0005
TS-aMEP	2.9 ± 1.0	6.2 ± 3.0	0.00004	3.1 ± 1.0	4.9 ± 1.7	0.004
TL-rMEP	2.7 ± 1.0	5.6 ± 2.0	0.003	2.7 ± 1.0	5.7± 2.8	0.005
TS-rMEP	3.0 ± 1.1	7.1 ± 1.5	0.01	2.8 ± 0.9	5.8 ± 1.6	0.04
PNTML	1.8 ± 0.1	4.1 ± 2.1	0.015	1.9 ± 0.5	3.7 ± 1.2	0.003

S1811

The Neurophysiology of Gastric Sensation in Functional Dyspepsia: Role of Abuse History and Somatization

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Background Abuse history and somatization are prevalent in Functional Dyspepsia (FD), but the exact nature of the relationship between both is incompletely understood. Abuse history influences neural correlates of rectal distension in Irritable Bowel Syndrome (Ringel et al, DDW 2006), but this has not been studied in FD; neither has the influence of somatization. *Aim* To study the influence of abuse history & somatization on neural correlates of gastric distension in FD. *Methods* Brain $H_2{}^{15}O$-PET was performed in 25 FD patients (mean age 33) during 3 conditions (random order): no distension (baseline), isobaric distension at individual discomfort threshold (discomfort) & sham distension. Somatization (PHQ-15) & abuse history were measured using validated self-report questionnaires. Data were analyzed with threshold p_{uncor} <0.001 (SPM2). Abuse history & somatization were correlated with mean brain activation during baseline, distension and sham as well as with the mean differences in activation distension-baseline and sham-baseline. *Results* Behavioural Mean score for somatization was 15±1, with 15 being the cutoff for "high" (Kroenke 2002). Eight patients (32%) reported an overall history of abuse; this was associated with significantly higher somatization scores (19±2 v.s 13±2, p=0.01). Imaging results are summarized in the table. Significant correlations were found between abuse history and activation in mainly (para)limbic areas involved in affective regulation, including hippocampus, amygdala, orbitofrontal cortex and insula. Somatization mainly correlated with brainstem (medulla), cerebellum, cingulate subregions and higher-order association areas. *Conclusion* In FD, brain activation during baseline, gastric distention and sham is influenced by abuse history and somatization. These findings provide neurobiological correlates for psychosocial influences on gastric sensation and their involvement in FD pathogenesis.