which initiates inflammatory events; and (c) increased intercellular adhesion molecule-1 (ICAM-1) and interleukin-6 (IL-6) levels ($p<0.05$). In addition, high amount of conjugated dienes and malondialdehyde along with significantly reduced superoxide dismutase activity were noted in the intestine of IR subjects, which indicates the presence of oxidative stress ($p<0.05$). Moreover, exposure of the intestine of IR subjects to proinflammatory lipopolysaccharides (LPS) or oxidative stress conditions unraveled an abnormal response magnitude. Indeed, IL-6 and conjugated dienes levels were further increased in presence of LPS and pro-oxidant conditions, respectively, in the intestine of IR subjects compared to IS subjects ($p<0.05$). Finally, the intestine of IR subjects showed increased de novo lipogenesis rate, higher expression of fatty acid binding proteins (L-FABP and I-FABP) and microsomal transfer protein (MTP), and stimulation of apo B-48 biogenesis, which collectively contributed to the exaggerated triglyceride-rich lipoprotein secretion ($p<0.05$). Conclusion: Small intestine of IR obese subjects exhibits several markers of inflammation and oxidative stress in association with local insulin resistance and lipoprotein overproduction. These abnormalities may likely contribute to the development of diabetic dyslipidemia and evolution of the metabolic syndrome.

Tu1751

Octreotide Promotes Weight Loss via Suppression of Intestinal MTP and ApoB48 Expression in Diet-Induced Obesity Rats

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Background and aims: The aetiology of obesity is multi-factorial, but it is widely accepted that dietary fat is an important contributor. Dietary fat is mostly taken up in the intestine and transported into the circulation in the form of chylomicrons, which involving the participation of Apolipoprotein B48 (apoB48), microsomal triglyceride transfer protein (MTP) and apolipoprotein AIV (apoAIV). Previous research found that overproductions of apoB48, apoAIV and MTP might lead to excessive lipoprotein production or dietary fat absorption. However, little is known about the changes of these proteins in response to a chronic high-fat diet and whether these changes are associated with obesity. SST and its analogues such as octreotide have been used in trials in patients with pediatric hypothalamic obesity and obese adults with insulin hypersecretion. However, its application for diet-induced obesity has not been systematically investigated. The aim of this study was to investigate the expression levels of intestinal apoB48, MTP and apoAIV in high-fat diet induced obesity rats and the possible effect of octreotide on them. Methods: SD rats were asigned into the control group and the high-fat diet group. Obese rats from the high-fat diet group were further divided into an obese group and an octreotide-treated group. Rats in the octreotide-treated group were subcutaneously injected with octreotide for 8 days. Body weight, fasting plasma glucose (FPG), fasting serum insulin, triglyceride (TG), total cholesterol (TC) and high density lipoprotein-cholesterol (HDL-C) were measured. Intestinal MTP, apoB48 and apoAIV expression levels were determined by real-time PCR, western blot or ELISA analysis. Results: The high-fat induced obesity rats express more apoB, MTP and apoAIV mRNA as well as apoB48 and MTP protein in the intestine than normal control rats. This observation occurred along with increased body weight, FPG, TG, TC, fasting serum insulin and the derived homeostatic model assessment (HOMA) value. Octreotide intervention significantly decreased body weight and the blood parameters, and downregulated expression of apoB mRNA and apoB48 protein, as well as MTP mRNA and proteins, but had no significant effect on apoAIV mRNA levels. Conclusion: High-fat diet induced obesity is associated with increased expression of apoB48, MTP and apoAIV in the intestine. Octreotide intervention inhibits the over-expression of apoB48 and MTP, and consequently brought about reduced fat absorption and weight loss.

Tu1752

Effect of Satiety Hormone Analog, Exenatide, on Resting State Brain Activity

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Background: Exenatide is the medically relevant analog of GLP-1, an endogenous hormone associated with feelings of satiety. GLP-1 increases after Bariatric surgery and is hypothesized to be involved in successful weight loss. Potential drug-induced changes in the brain have largely been unexplored. Aims: To investigate the potential effect of Exenatide on the resting brains of lean, healthy women using a resting state analysis technique that looks at shifting of frequency patterns in the brain. Based on previous frequency analyses and the literature on GLP-1 and satiety, we hypothesize the drug to show an altered pattern of frequency band power in areas of the brain involved with hunger and emotional arousal. Methods: Resting state scans were taken of 7 healthy female subjects using a Siemens Allegra 3T MRI scanner after at least 8 hours of fasting. In a two-day double-blind crossover design, ten minute scans during which the subject was asked to lay quietly, eyes closed but not fall asleep were run before, 10min. and 30min. after the subcutaneous injection of 5ugs of Exenatide or saline placebo. Normalized fractional amplitude of low frequency fluctuations (fALFF) maps were created for frequency bands in .073-.198hz (Slow-3), .027-.073hz(slow-4), and .01-.027 (slow-5) ranges. A flexible factorial design was applied to both days to test for shifting of the distribution of frequency power among these bands in regions of interest (ROIs) using type I error rate of 5%. ROIs were chosen based on their association with hunger or emotion networks. Results: After injection of the Exenatide drug, frequency shifts from the lower to higher frequency bands were seen in the right lateral prefrontal cortex (PFC) and thalamus. Shifts from higher to lower bands were observed in the left anterior cingulate cortex, orbitomedial PFC, and the basal ganglia. A different pattern was observed during the placebo day where shifts from lower to higher frequency bands were observed in the left ventrolateral PFC, bilateral mid insula, right posterior insula, right hippocampus, and left dorsolateral PFC and shifts from higher to lower frequency bands were seen in the brainstem, left nucleus accumbens, basal ganglia, bilateral thalamus, left anterior cingulate, left amygdala, left dorsomedial PFC, left dorsolateral PFC, and right hypothalamus. Discussion: Shifts in the frequency bands in brain regions associated with satiety and emotional arousal were observed more during the placebo day then as an effect of the Exenatide drug. This provides evidence of a dampening the drug may have on the usual brain changes that occur over a long scanning session in which subjects show changing activity in brain regions suggestive of a hungry state. This implies that this drug does have an impact on the brain that may lead to the feelings of increased satiety associated with weight loss.

Tu1753

Central Functions Altered by Chronic High-Lipids Diets Enriched With Omega-3, Omega-6 or Saturated Fat

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High-fat diets consumption induces low-grade obesity-related inflammation (Clark et al, 2011). The blood-brain barrier (BBB) can be damaged by immune cells invasion facilitated by pro-inflammatory cytokines. Interestingly, omega 3 fatty acids inhibit the production of pro-inflammatory cytokines, and omega 3 fatty acids supplementation (DHA) can increase the activity of the prefrontal cortex, which is one of the brain areas that was found deactivated in obese humans and minipigs (Val-Laillet et al, 2011). We hypothesized that a diet enriched with omega 3 might prevent the onset of central inflammation and protect some brain areas that are important for food intake control. We decided to investigate this question in 15 obese minipigs fed with high-fat diets of which the lipids were provided by either fish oil rich in omega 3 (O3), sunflower oil rich in omega 6 (O6), or lard rich in saturated fat (S). Various measures were performed on these animals, including adiposity estimation by CT-scan, BBB permeability evaluation by dynamic injected CT-scan, and brain metabolism exploration by Positronic Emission Tomography (PET). After five weeks of treatment, there was no significant difference between groups for the body weight, adiposity accumulation and distribution ($P>0.10$). The BBB was the most permeable in the O3 group, intermediary in the S group, and the least permeable in the O6 group for the cortical areas ($P=0.0326$ for O3 vs O6 - Fig. 1). Basal metabolism differences were found in several brain regions involved in food intake control. For example, the anterior prefrontal cortex metabolism was lesser for O3, intermediary for S, and higher for O6 (Punc <0.0001 - Fig. 2). There was also a decreased activity in the nucleus accumbens (Punc=0.038) for O3 compared to O6. There was a significant correlation between the BBB permeability and the prefrontal cortex activity ($R=0.55$, $P=0.041$ - Fig. 3). Contrary to what was expected, these results demonstrate that a diet enriched with O3 did not protect the BBB nor the basal metabolism of brain areas (e.g. prefrontal cortex and basal nuclei) usually altered by obesity and high-fat diets. Surprisingly, the O6 diet induced the least damage to the BBB and deactivation of the prefrontal cortex and nucleus accumbens. Further research is needed to elucidate whether a causal relationship between these two phenomena exists, and why the O6 diet, unlike O3, had this protective effect.

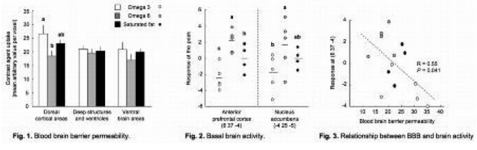

Fig. 1. Blood brain barrier permeability. Fig. 2. Basal brain activity. Fig. 3. Relationship between BBB and brain activity

Tu1754

Ghrelin Induces Leptin Resistance by Activation of cAMP-Epac-SOCS3 Signaling: Implications in Satiety Regulation

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The anorexigenic adipocyte derived hormone, leptin and orexigenic hormone, ghrelin, act in opposition to one another to regulate feeding behavior. However, the mechanism by which ghrelin exerts its inhibitory effects on leptin has not been elucidated. We hypothesize that ghrelin activates Epac, the exchange protein activated by cAMP, resulting in increased SOCS3 (suppressor of cytokine signaling) expression which negatively impacts leptin signal transduction and neuronal firing in the nodose ganglia (NG) neurons. Double immunostaining studies showed that the leptin receptor (LRb) was expressed in 47 ± 2% of NG neurons. The ghrelin receptor (GSHR1a) was expressed in 41 ± 3% of NG neurons and 87 ± 5% of these receptors co-localized in leptin expressing NG neurons. Western blot analysis demonstrated that leptin (0.01-100nM) caused a dose dependent increase in STAT3 phosphorylation which was maximal at 1 nM. Ghrelin (10nM) significantly inhibited leptin(1nM) stimulated STAT3 phosphorylation by >65%. Ghrelin (10nM) also significantly inhibited Janus kinase2 (JAK2) phosporylation by >80%. To investigate the signaling cascades utilized by ghrelin, we showed that transient transfection of cultured NG neurons with SOCS3 siRNA or Epac siRNA to silence the SOCS3 and Epac genes, reversed the inhibitory effects of ghrelin on leptin stimulated STAT3 phosphorylation. Ghrelin (10nM) alone caused a significant 2 fold increase in both Epac and SOCS3 expression in cultured rat NG neurons. Transfection of the NG neurons with Epac siRNA prevented an increase of SOCS3 evoked by ghrelin. Patch clamp studies using isolated NG showed that leptin (10 nM) generated an inward current of 38 ± 8 pA in 8/24 neurons tested. Ghrelin (10nM) markedly inhibited leptin stimulated neuronal firing, reducing the inward current to 12 ± 5 pA in 6/22 of neurons tested. The IV relationship plot showed the currents reversed at -100 mV for each peptide, which is close to the K^+ equilibrium potential (~105 mV). Silencing of the STAT3 gene completely abolished leptin stimulated neuronal firing. Silencing of the SOCS3 gene reversed the inhibitory effects of ghrelin on leptin-stimulated neuronal firing. We conclude that ghrelin exerts its inhibitory effect on leptin stimulated STAT3 phosphorylation by increasing Epac expression which leads to increased SOCS3 activation. Ghrelin stimulated SOCS3 negatively feeds back by binding to JAK2, leading to decreased phosphorylation of both JAK2 and STAT3. Leptin mediated phosphorylation of STAT3 activates the closure of the ATP-sensitive K^+ voltage channel, leading to membrane depolarization and neuronal firing. This was significantly inhibited by ghrelin. The Epac/SOCS3 signaling pathway played a pivotal role in ghrelin's inhibitory effect on STAT3 phosphorylation and neuronal firing. Malfunctioning of these signaling molecules may result in eating disorders.