transcriptional disease mechanism for altering muscle phenotype in human type 2 diabetes

Mootha VK, Lindgren CM, Eriksson KF, Subramanian A, Sihag S, Lehar J *et al*. (2003). Nat Genet 34, 267-273.

Patti ME, Butte AJ, Crunkhorn S, Cusi K, Berria R, Kashyap S *et al*. (2003). Proc Natl Acad Sci U S A 100, 8466-8471

Timmons JA, Wennmalm K, Larsson O, Walden TB, Lassmann T, Petrovic N *et al*. (2007). Proc Natl Acad Sci U S A 104, 4401-4406.

The clinical cohort study was supported by the Danish National Research Foundation Grant DG 02-512-555 (BKP). This study was supported by an Affymetrix Translational Medicine award (JT), the Swedish Diabetes Association (JT) and the Chief Scientists Office Scotland (JT). GH is a Wellcome Trust CD fellow. JR is supported by the SIROCCO FP6 program.

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C13 and PC23

Increased energy intake in children with an obesity-associated FTO gene variant

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C14 and PC24

Illness, body mass index and leptin

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Introduction
There is anecdotal evidence that obese individuals suffer from poor wound healing and frequent minor illnesses such as upper respiratory tract infections (URTI) cf. lean individuals. The altered metabolic, psychological and endocrine status of obesity may lead to immunodepression. Our group has investigated URTI in fatigued athletes and military personnel (Castell, 2003); one study focused on the obesity hormone, leptin which regulates energy balance, and its role in immune function. Decreased circulating leptin can lead to hyperphagia in some genetically obese individuals (O'Rahilly, 2002). However, human obesity is usually characterized by excessive leptin, rather than deficiency. The leptin functional receptor is found in all immune response cell types: thus leptin may link nutritional status, energy balance and immune function. Sleep loss, partial or chronic, is linked to decreased immune function. Obesity is a factor in obstructive sleep apnoea, which significantly reduces sleep duration and quality.

Aims
This pilot study surveyed the incidence and severity of URTI, psychological and sleep profiles in sedentary participants of different ages, and body mass indices (BMI). The aim was to observe whether mild obesity (BMI 30-35) predisposed people to an increase in URTI cf. individuals with a lower BMI. The survey was a precursor to a more detailed study.
Methods
Eight lean, 2 overweight, 8 obese sex matched, sedentary participants were recruited for this ethically approved survey. Anthropometrics (ht, wt, waist, hips) were taken; A resting blood sample measured plasma leptin; Daily questionnaires were given for 6 wks to monitor URTI; POMS (depression, stress, fatigue, motivation); Sleep (duration, quality); Dietary diaries. A multiple regression General Linear Model was used to explain the "illness score".
Results
A higher BMI was significantly associated with higher symptoms of illness ($p<0.01$). Calorie consumption was associated with BMI ($p<0.05$). BMI correlated with plasma leptin concentration. Poor sleep quality predisposed individuals to an increase in URTI symptoms ($p<0.032$); in addition it was associated with higher levels of depression ($p<0.005$) and stress ($p<0.005$). Sleep duration did not have any effects.
There was an apparent link between smoking and increased URTI symptoms.
Discussion
The study showed links between increased BMI, poor sleep quality and the incidence of self-reported URTI. It is suggested that obesity is associated with an increase in URTI cf. normal or lean weight. BMI was linked with blood leptin concentration, and it is tempting to speculate that there might be a link between leptin and increased URTI.

Castell LM (2003) Sports Med 33: 323-345

O'Rahilly S (2002) Nutr Rev 60: S30-S34

We are grateful to the volunteers for their cheerful participation

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PC3

The role of peripheral and central chemoreceptors in the hypermetabolism-induced increases in the ventilatory chemosensitivity to CO_2 in humans

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The role of hypermetabolism in the mediation of exercise hyperpnoea is contentious. Recent animal data has shown that the carotid body may be directly involved in establishing the hyperpnoea via a metabolic rate (MR)-induced elevation in the ventilatory sensitivity to CO_2 (Bin-Jaliah et al., 2005). A previous human study had also evidenced augmented chemosensitivity to CO_2 in response to raised MR, yet no inferences were made on the potential role that peripheral chemoreception could have played on these observations (Zwillich et al., 1977). Therefore we aimed to appraise the importance of peripheral chemoreception in the hypermetabolism-induced increases in chemosensitivity in awake humans.

Fourteen healthy subjects took part in either one of two separate experiments. Local ethical approval was obtained and all subjects gave written informed consent. Each experiment involved a different methodology to assess the ventilatory response to euoxic ($PetO_2$ = 100mmHg) hypercapnia before and 210 minutes after the ingestion of a fixed amount of food; a five-minute ramp protocol ($PetCO_2$ = 0 to 8 mmHg above normal; n=7) in which peripheral chemoreception has been known to play an important role, and a step change protocol ($PetCO_2$ = 0, 2, 4, 6 and 8 mmHg above normal; each step lasting 3 minutes; n=7) in which the role of central chemoreceptors is predominant. MR was measured as oxygen consumption prior to each challenge of hypercapnia. Data were analysed by means of paired t-tests (SPSS 16.0) and significance was taken at $p<0.05$.

All data are expressed as mean±S.E.M. MR was significantly increased by food ingestion in both experiments ('Ramp' experiment; 0.22±0.02 to 0.30±0.02; 'Step' experiment; 0.25±0.01 to 0.30±0.02, baseline vs 210 min, All $P<0.03$). The ventilatory sensitivity to CO_2, was increased significantly in the ramp protocol (1.13±0.11 to 1.78±0.15 L/min/mmHg, baseline vs 210 min, P=0.0001) but, although the mean was elevated, the sensitivity to CO_2 was not significantly increased in the step protocol (1.14±0.13 to 1.42±0.22 L/min/mmHg, baseline vs. 210min, P=0.26).

Our results suggest that the hypermetabolism-induced increases in the ventilatory sensitivity to CO_2 might be primarily mediated through elevations in the peripheral chemoreceptor gain. Enhancement of this gain appeared to be facilitated even by mild increments of MR. The mechanism that couples metabolism to changes in chemosensitivity is not known.

Bin-Jaliah, I. et al. (2005). J Physiol, 563, 883-893.

Zwillich, C.W. et al. (1977). J Clin Invest, 60, 900-906.

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PC4

Nociceptin/Orphanin FQ peptide (NOP) receptor and its involvement in regulation of food intake

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The incidence of obesity and related co-morbidities is rapidly growing, and the need for novel efficacious treatments is pressing. Nociceptin/Orphanin FQ, an endogenous orexigenic peptide for the G protein-coupled receptor, NOP (previously known as opioid-like receptor 1 (OLR-1)) has been recently identified as a therapeutic target for obesity. Antagonists of the NOP receptor have been shown to selectively block N/OFQ-induced food intake (for review please see [1]).

The primary objective of our research is to delineate discrete chemically defined NOP receptor expressing neuronal populations critically affecting food intake and body weight. N/OFQ and its receptor, NOP, are diffusely expressed in the dorsal raphe nucleus (DRN), a brain region containing a critical population of serotonin (5-HT) neurons, as well as other brain regions associated with satiety. The 5-HT system is well established in food intake regulation. We hypothesize that N/OFQ is an upstream modulator of 5-HT bioavailability in DRN, a neurotransmitter system targeted for the treatment of obesity.

The anatomical distribution of NOP receptor in DRN lends circumstantial support to a role for this neuropeptide in the CNS regulation of ingestion. We hypothesize that N/OFQ and 5-HT are not co-expressed in the DRN, but rather that N/OFQ is released locally within the DRN and inhibits the action of 5-HT neurons via NOP receptors. To examine co-expression of N/OFQ and 5-HT in the DRN, we performed dual-immunohistochemical labelling using a rabbit anti-N/OFQ antibody (Phoenix, 1:1000) and a goat anti-5-HT antibody (Chemicon, 1:1000) using rat brain tissue. Our results show very few neurons co-expressing N/OFQ and 5-HT.

Additionally, under conditions of food deprivation/hunger, the NOP receptor has been shown to be bilaterally and significantly down-regulated in the paraventricular nucleus of hypothalamus (PVH) and central nucleus of the amygdala (CeA). To test our hypothesis that NOP receptors expressed in DRN are also involved in regulation of feeding, we investigated whether the NOP receptor is nutritionally regulated in the DRN. By performing in situ hybridization histochemistry we observed, like in the amygdala and hypothalamus, a significant down-regulation of NOP receptors in the dorsal raphe nucleus in response to food deprivation/hunger.

In future experiments, we will investigate the effect of basal and N/OFQ-induced feeding in selective DRN NOP receptor null rats. We will compare the DRN NOP receptor null phenotype with that obtained following global brain NOP receptor ablation and site specific NOP receptor deletion in classic regions associated with satiety.

Data generated in this proposal will help elucidate critical NOP receptor expressing populations affecting ingestive behavior