Obesity is widely recognized as the largest and fastest growing public health problem in the developed and developing world.

This three day event will discuss aspects of obesity development and treatment in an informal academic setting. With plenty of opportunity for networking and debate, this informal international meeting will bring you up to date with current research and thinking regarding obesity.

This event has **CPD accreditation**
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Poster Presentations

CLINICO-ECONOMIC ANALISIS OF METABOLIC SYNDROME’S TREATMENT
Day 1 Morning Session: Predicting obesity for the development of diagnosis and management

Invited Speakers Abstracts

Obesity and metabolic health status: predictive gene signatures
Dr Janice E. Drew, Senior Research Fellow, University of Aberdeen, UK
Obesity leads to disrupted cell defence systems, immunity, inflammation, redox regulation, metabolism and DNA repair, which are required for maintenance of health. It is now a feasible prospect to determine predictive markers in human blood that are associated with health status in obese individuals using recent innovations in gene expression profiling technologies. Strategies to investigate cell defence system gene expression profiling of human whole blood and the opportunities this presents to predict health status and benefits conferred by diet will be presented.

How much do we eat: From Diet Surveys to Biomarkers of Intake
Professor Jack Winkler, London Metropolitan University, UK.
The obesity epidemic is evidence of a serious problem with our diet. Nutrition science has a serious problem too – we cannot measure accurately what people eat. This compromises our ability to understand what causes obesity and how to reverse it.
Diet surveys all rely on subjects telling researchers honestly what they eat. But they do not. Most people claim to be eating a healthier diet than they actually do, lower in volume and a more nutritious mix. This is known in the trade as “under-reporting”. In plain English, they lie.
The scale of misinformation is large. For example, in the US national survey, NHANES, over 60% of respondents claim to be eating less than is necessary to stay alive.
To correct the problem, we need measures of food consumption that are independent of the “self-reports” of subjects. We need physiological, biochemical or genetic biomarkers of intake.
At present, we have two that provide acceptable measures – “double-labelled water” for total calories and 24-hour urine studies for sodium. There are technical issues with both, but the real issues are that they too expensive and administratively complicated to use on large-scale national surveys. So they are used on small sub-samples, or not at all.
But the critical need is for valid, reliable, inexpensive and non-intrusive measures of all the macro- and micronutrients. And we need technical developments to ensure that the results are reported without opportunities for adjustment by subjects.
Much research is underway to develop biomarkers of intake. The lecture will describe the current state of work and its relevance to obesity.

The association of abdominal obesity with cardiometabolic risk biomarkers in men and women of two urban groups of African origin: Cotonou (Benin) and Port-au-prince (Haiti)
Asma El Mabchour TRANSNUT, Department of Nutrition, University of Montreal, Montreal (Québec), Canada
Abdominal obesity (AO) is a central factor of metabolic syndrome. It increases in low income countries. Its relationship with cardiometabolic risk biomarkers (CMRB) varies with race-ethnicity groups. Objective: to assess the prevalence of AO and its association with the other CMRB in two urban African origin groups, Cotonou (Benin) and Port-au-Prince (Haiti). AO was higher in Cotonou than in PAP and in women than men. The association of AO with other CMRB varied markedly between the two groups and according to sex. Further research on specific WC cut-offs for African origin populations is therefore warranted.
The Effect of Exercise On the Problem Of Obesity,  
Dr Edward R. Laskowski, Professor, Department of Physical Medicine and Rehabilitation, Mayo Clinic  
Co-Director, Mayo Clinic Sports Medicine Center, USA  
Significant research has been performed on the effects of exercise for the reduction of body weight, with most studies indicating that exercise alone has a small effect on body weight reduction independent of caloric restriction. When combined with dietary restriction, exercise has a synergistic effect and enhances weight loss beyond the effect of diet alone. Exercise also has been shown to have significant beneficial effects on cardiovascular and metabolic risk factors independent of actual weight loss. Genetic factors related to obesity have been found to be positively modified when individuals incorporate physical activity into their lifestyle. Exercise is essential for the prevention of weight gain over a lifespan.

Adipose tissue development and fetal programming of later obesity  
Professor Michael E Symonds, Deputy Head of The School of Medicine, Director of Infrastructure and Personnel Director of the Early Life Research Unit, Academic Division of Child Health, Obstetrics & Gynaecology School of Medicine Queen's Medical Centre University Hospital The University of Nottingham, UK  
Impact of early life nutritional supplementation on cardiometabolic risk of young adults from a transitional rural community in India: Andhra Pradesh Children and Parents Study (APCAPS)  
Dr Sanjay Kinra, LSHTM, London, UK  
The Andhra Pradesh Children and Parents Study (APCAPS) was established through the long term follow up children born in a nutrition supplementation trial, in which protein-calore supplement was given to pregnant women and young children. During 2009-12, 1860 index trial children were re-examined at the mean ages of 22 years: those who received nutritional supplementation in early life had lesser arterial stiffness and carotid intima media thickness compared to controls, despite higher blood pressure and cholesterol levels, suggesting that early life undernutrition may predispose to premature atherosclerosis and cardiovascular disease.

Poster Presentation Abstracts

MR-PROADM PLASMA LEVELS ARE INCREASED IN OBESE ADOLESCENTS  
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Background: Studies on adipokines and other biomarkers of obesity have became important in obesity research and recently also adrenomedullin (ADM) was defined as a new member of adipokine family. The ADM precursor gene, (preproADM) is transcriptionally induced by insulin, hypoxia and inflammatory stimuli and acute hyperinsulinemia was associated with increased circulating plasma ADM levels in diabetic patients or in uncomplicated obese subjects. It has been shown that ADM can be beneficial in treating some diseases such as hypertension, cardiac hypertrophy, cerebral ischemia. Thus, ADM secreted by adipocytes, through its vasodilator and antioxidant actions, might be protective against cardiovascular complications induced by metabolic syndrome. To date, little is known on the impact of obesity on plasma ADM and no data are available for this peptide in childhood obesity. Aim of the present study was to assess plasma MR-proADM levels in obese adolescents compared with normal weight subjects and its relation with weight and BMI.
**Methods**: Plasma MR-proADM was measured in 30 healthy adolescents (BMI=20.9±0.6) and in 51 age-matched obese adolescents (BMI=29.6±0.6) by a Time-Resolved Amplified Cryptate Emission (TRACCE) technology assay, using a kit designed for automated sandwich immunofluorescent assay of MR-proADM (KRIPTOR: BRAHMS AG).

**Results**: Plasma MR-proADM levels resulted significantly higher in obese than in healthy adolescents (MR-proADM: 0.33±0.1 vs 0.40±0.1 pmol/L, p<0.0001). Circulating MR-proADM levels correlated to body weight (r= 0.35, p=0.002), BMI (r= 0.53, p<0.0001) and with fat mass (r=0.51, p<0.0001) while no correlation was observed with lean mass (r=0.05, p=0.6). A significant correlation was also observed with insulin levels (r=0.3, p=0.007) and with systolic blood pressure (r=25, p=0.02). Plasma MR-proADM levels were not related to gender or age.

**Conclusions**: Our results showed, for the first time, an increase in circulating MR-proADM plasma levels in obese adolescents confirming previous data observed in adults. The pathophysiological role of adipose tissues-secreted ADM is still speculative and further studies are necessary to clarify its effect, particularly in obesity. If the hypothesis of its beneficial effect is confirmed, then ADM might be useful in developing drugs to prevent cardiovascular complications associated with obesity.

**TRANSCRIPTIONAL ALTERATIONS OF ET-1 SYSTEM IN LUNG TISSUE OF OBESE ZUCKER RAT**.

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**Background**: Obesity is a complex pathology with interacting and confounding causes due to the environment, hormonal signalling patterns and genetic predispositions. It is an independent risk factor for cardiovascular disease, which can dramatically increase the likelihood of negative outcomes. Recently, obesity has been implicated in the development of many carcinomas, and its prevalence is reaching epidemic proportions in children and teenagers. The endothelin (ET) axis has been shown to have a role in the growth and progression of several tumour types including lung cancer. Aim of this study was to evaluate the ET-1 system transcriptional alterations associated to the obesity in lung tissue of Zucker rats.

**Materials and Methods**: Two groups of Zucker rats, 9-13 weeks, were studied: obese rats (O, n=20), and controls (CO, n=20). Half of them were studied under fasting conditions (CO_f, O_f) and the remainders after the induction of acute hyperglycemia (CO_ag, O_ag). The cDNA was synthesized with an iScript cDNA Synthesis kit (Bio-Rad, Hercules, CA, USA) using about 1 µg of total RNA as template. Real-Time PCR reactions were performed in duplicate in the Bio-Rad C1000™ thermal cycler (CFX-96). The experimental results were normalized with the three most stably expressed genes (YWHA, SDHA, ACTB).

**Results**: Significantly higher prepro-ET-1 (p=0.05) and ECE-2 mRNA expression was observed in O with respect to CO. ECE-1 mRNA expression resulted undetectable in the lung tissue of Zucker rats while ET-A and ET-B resulted to be expressed at similar levels both in CO and in O. When the two groups were further subdivided in fasting and hyperglycemic rats any significantly difference was not observed in the transcriptomic profile of ET-1 system between CO and O although O_ag showed a more marked expression pathway than in all other groups. A significantly correlation was observed between ET-A and ET-B (p=0.04) as well as between prepro-ET-1 and ET-A (p=0.009).

**Conclusion**: ET-1 overexpression, together with the ET-A and ET-B upregulation observed in O_ag, are in line with previous studies on solid tumors and suggest to evaluate, in the lung of these animals, the presence of any genomic damage. The study of ET axis and, in particular, ET receptor antagonism, may provide an important tool to modulate the inappropriate secretion of this peptide in pathological conditions providing the key to a new generation of chemotherapeutic agents.
ENDOTHELIN SYSTEM MRNA VARIATION IN THE HEART OF ZUCKER RATS: EVALUATION OF A POSSIBLE BALANCE WITH NATRIURETIC PEPTIDES

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Background: The deregulation of neurohormonal systems, including the natriuretic peptide (NP) and endothelin (ET) systems, may increase the possibility of developing obesity-related risk. The aim of our paper was to evaluate ET system mRNA variation in heart of the Zucker rat model together with the simultaneous evaluation of the NP system transcriptomic profile. In order to analyze the link between the ET-1 system and the inflammatory process, the cardiac expression of interleukin (IL)-6 and tumor necrosis factor (TNF)-α was also measured.

Methods and Results: Zucker rats of 9-13 weeks were subdivided into obese rats (O, n=20), and controls (CO, n=20): half of them were studied under fasting conditions (COfc-Ofc) and the remainder after the induction of acute hyperglycemia (COAH-OAH). Cardiac mRNA expression of TNF-α, IL-6, NP/ET-1 systems was evaluated by Real Time-PCR. No significant difference for pre-proET-1, ET-A and ET-B mRNA expression was detected between O and CO; whereas significantly lower mRNA levels of the ECE-1 were observed in O (p=0.02). Regarding NPs, only BNP mRNA expression decreased significantly in O with respect to CO (p=0.01). A down-regulation of NPR-B and NPR-C and an up-regulation of NPR-A was observed in O. No significant difference for IL-6 and TNF-α mRNA was revealed. Subdividing into fasting and hyperglycemic rats, many of the genes studied maintained their mRNA expression pattern almost unchanged.

Conclusions: The modulation of ET-1/NP systems in obesity could be a useful starting point for future studies aimed at identifying new therapeutic strategies for the treatment of cardiometabolic syndrome.

Day 2 Afternoon session - Fetal programming of body composition, obesity, and metabolic function

Invited Speakers Abstracts

The role of developmental programming in the development of fatty liver
Dr S Carr, University of Cambridge Metabolic Research Laboratories, Institute of Metabolic Science, University of Cambridge, Cambridge, UK

The importance of the in utero and postnatal environment on the offspring health is well documented. Both under and over nutrition has an important role in programming deleterious effects in the offspring. However, the molecular mechanisms mediating these effects remain poorly understood. Using the well characterised rodent model of maternal protein restriction, large differences in longevity have been observed. Offspring exposed to a low protein diet during pregnancy (recuperated animals) have a significantly shorter lifespan than controls. Using a genome wide microarray approach in the liver, genes were identified that had differentially expression in response to maternal diet throughout the life course. One of the most interesting genes is cell death-inducing DFFA-like effector a (Cidea), a gene implicated in lipid accumulation, as expression is only induced at old age, but this was exaggerated three fold in the recuperated offspring. Using a genome wide microarray approach in the liver, genes were identified that had differentially expression in response to maternal diet throughout the life course. One of the most interesting genes is cell death-inducing DFFA-like effector a (Cidea), a gene implicated in lipid accumulation, as expression is only induced at old age, but this was exaggerated three fold in the recuperated offspring. These offspring demonstrated increased hepatic lipid accumulation along with higher levels of transcription factors and genes important in lipid storage. In vitro analysis revealed that Cidea is activated by oxidative stress, which was also seen in the recuperated offspring. These changes effects hepatic lipid metabolism in these animals and thus provides a mechanism by which maternal diet can contribute to the metabolic health and ultimately the life span of the offspring.
Breaking the intergenerational cycle of obesity through nutritional interventions in pregnancy and infancy

Dr Bev Muhlhausler, Head Obesity and Metabolic Health Division, FOODplus Research Centre, University of Adelaide, Australia

A world-wide series of human and experimental animal studies have provided compelling evidence that the pathway to obesity can begin very early in life, and that exposure to a sub-optimal nutritional environment during critical windows of development before birth and in early infancy can increase an individual’s susceptibility to obesity in child and adult life. This presentation will focus on work from our group and others which has shown that nutritional interventions during pregnancy and/or infancy has the potential to improve metabolic outcomes in the offspring, and could potentially break the current intergenerational cycle of obesity and poor metabolic health.

Study of maternal dietary fatty acids quality in pregnancy for the modulation of adiposity in the offspring

Dr Alicia Leikin-Frenkel, Sackler School of Medicine, Tel Aviv University and The Bert W. Strassburger Lipid Center, Israel

Despite the well established importance of early nutrition in the programming of adult disease, the contribution of fatty acids remains unclear. The influence of maternal diets enriched in n-3 or saturated fatty acids (SFA), on the early signs of adiposity and insulin resistance of their offspring was tested in a mouse model. The results showed early signs of inhibition or stimulation by n-3 or SFA, respectively, of insulin resistance and fat accumulation, measured by genetic and biochemical determinations. We conclude that maternal fatty acids quality in pregnancy have a role in the promotion of health or disease in the offspring.

Perinatal programming of obesity and epigenetic outcomes,

Paul Cordero, Department of Nutrition, Food Science and Physiology. Faculty of Pharmacy. University of Navarra, Spain.

Paul Cordero carried out his Pharmacy degree and the European Master of Metabolism and Nutrition at University of Navarra, Spain. There, he obtained his PhD in Pharmacy, October 2012, at the Department of Nutrition, Food Science and Physiology. His research has been focused in the epigenetic regulation of transcriptomic profile in animal models of obesity and its comorbidities, as well as in the search of epigenetics biomarkers of diet response in human beings. During his career he has carried out different stays at Santo Antonio Hospital (Porto, Portugal), Catalan Institute of Oncology (Barcelona, Spain) and University of Cambridge (Cambridge, UK).

Day 2: Gene-environment interactions in obesity

Invited Speakers Abstracts

Gene-environment interactions in the triangular relationship between obesity, depression and cardiovascular disease

Dr Lucy F. Faulconbridge, Assistant Professor of Psychology in Psychiatry, University of Pennsylvania, USA

A triangular relationship exists between obesity, depression and cardiovascular disease (CVD). A bi-directional relationship exists between obesity and depression, and each disorder is independently associated with incident CVD. Not all obese individuals succumb to depression; nor does every depressed person develop obesity. Likewise there is wide variation in whether obese, or depressed, individuals, are vulnerable or resistant to CVD. This talk will review the genetic and environmental pathways connecting obesity, depression, and CVD, and address how this research informs clinical practice. We conclude by identifying areas for future research and highlight the challenges of measuring the gene-environment interactions within and between each disorder.
Obesity resistance in selectively bred mice for high-running wheel behavior is reversed by perinatal cafeteria diet

Perinatal overnutrition predisposes offspring to obesity. To study whether physical activity (PA) is able to compensate this phenomenon, we exposed selectively bred hyperactive mice (S) and control (C) mice to combinations of pre/post-weaning cafeteria (CAF) diet and investigated energy balance parameters. While post-weaning CAF exposure caused obesity only in C mice, combined pre/post-weaning CAF exposure caused obesity and hyperinsulinemia in C as well as S mice, without affecting PA. Because obesity resistance in S mice is offset by perinatal CAF exposure despite maintenance of high PA levels, this suggests programming divergence of mechanisms controlling energy balance and voluntary PA.

Different expression of certain adipokines in subcutaneous and visceral tissues between obese and non-obese subjects and their correlations with clinical parameters and periphera metabolic factors.

*Dr Chantacha Sitticharoon*, Department of Physiology, Faculty of Medicine Siriraj Hospital, Mahidol University, Thailand

Expressions of certain adipokines are different between adiposity status as well as between subcutaneous and visceral adipose tissues. NPY, Y1R, and Y5R were higher in obese than in non-obese subjects while Y2R, serum adiponectin, and serum omentin-1 were higher in non-obese when compared to obese subjects. Visceral expressions of Y1R and Y5R were positively correlated with obesity and insulin resistance while subcutaneous expressions and serum levels of adiponectin and omentin were positively correlated to insulin sensitivity but negatively correlated to obesity. There might be different regulation of gene expression and adipokine secretion between obesity status and types of adipose tissue.

Prospective examination of DNA methylation and Obesity

*Dr L. Joseph Su*, National Institutes of Health, National Cancer Institute, USA

Obesity has been associated with increased risk of many of the non-communicable diseases, such as type-2 diabetes mellitus, hypertension, cardiovascular diseases and cancer. The rise of non-communicable diseases over the past two decades has occurred too rapidly to be solely explained by fixed genomic variation in combination with adult lifestyle factors. Alterations in epigenetic regulation of genes can lead therefore to profound changes in phenotype. In order to better understand the relationship between epigenetic process and obesity, DNA methylation data from a few prospective studies will be presented. Challenges and opportunities in future epidemiologic studies will be discussed.


*Dr Irene Maeve Rea*, Senior Lecturer and Consultant Physician Geriatric Medicine, Queens University Belfast and Belfast Health and Social Care Trust, Northern Ireland

Nutrition is widely believed to influence the ageing course with micronutrients playing a central role in metabolism and the maintenance of tissue function. Micronutrient nutrition has an enhancing effect on DNA repair in humans and has a profound influence on gene expression. Epidemiological evidence suggests an association between low consumption of fruit and vegetables and cancer with investigations supporting a role for the Mediterranean diet in having an ameliorating or preventative effect on cardiovascular risk. We have investigated some of these relationships in ‘elite’ nonagenarians from the BELFAST study who have aged well and avoided premature death from cardiovascular or cancer-related disease.

Genetic and Environmental Determinants of Comorbid Obesity in Major Psychiatric Disorders

*Dr Margarita Rivera*, Lecturer in Psychiatric Genetics, Institute of Psychiatry, King’s College London, UK

People with major psychiatric disorders (major depressive disorder, bipolar disorder, schizophrenia), particularly with mood disorders, have higher prevalence of comorbid obesity-related diseases, such as type 2 diabetes, metabolic syndrome and cardiovascular disease. The relationship between mental and physical disorders is complex and not clearly understood. Although it is well reported that these related diseases have a high impact in the lifespan and mortality of people with psychiatric disorders. Recent studies support the hypothesis that there may be shared aetiological factors, including genetic and environmental risk factors, between psychiatric disorders and obesity-related diseases. The talk will highlight the evidence of genetic and environmental risk factors implicated in the comorbidity of obesity-related diseases in major psychiatric disorders.
Obesity, leptin and respiratory control
Dr Mirian Bassi, Post-Doctoral, School of Dentistry, São Paulo State University (UNESP), Araraquara, Sao Paulo-Brazil
Evidence suggests that, in addition to regulate energy homeostasis and sympathetic activity, leptin also contributes to the CNS control of breathing. Obese transgenic leptin deficient (ob/ob) mice have an impaired respiratory response to hypercapnia that can be reverted by leptin treatment. Although the cellular basis for leptin effects on respiratory control is unknown, data from our studies have shown that melanocortin 3/4 receptors (MC3/4R), a system that play a pivotal role in mediated metabolic and cardiovascular actions of leptin, also can mediated leptin effects on ventilation. In addition, we demonstrated that leptin may act in an important nucleus located in the ventral chemorespiratory surface of medulla called retrotrapezoid (RTN) to induces these respiratory alterations.

Poster Presentation Abstracts

FELINE BODYWEIGHT: INFLUENCE OF GENETIC BACKGROUND ON BLOOD PARAMETERS OF ENERGY METABOLISM
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Introduction: Obesity is an increasing problem in domestic cats. Obesity and obesity-associated diseases like diabetes mellitus type 2 in companion animals are among the diseases with the fastest growing prevalence worldwide. This is also seen in humans. Besides food intake, food composition, and low activity, genetic factors are also believed to influence the development of obesity in cats. In the experimental cat population of the Institute of Animal nutrition a complex segregation analysis indicated a genetic influence on the striking obese phenotype. A whole-genome SNP association mapping identified three loci on chromosome D3 and C2 associated with body condition score in the experimental cat population. The associated regions on chromosome D3 contain MC4R and NPY1R as positional candidate genes. In an additional study with cats of the obese and lean phenotype of the experimental cat population the reaction of blood parameters of energy metabolism on the feeding of different rations a) high carbohydrate (HCH), b) high fat (HF) and c) high protein (HP).
Materials and Methods: In this study 13 adult, European short-hair, healthy tomcats from the experimental cat family of the Institute of Animal Nutrition of the Vetsuisse Faculty were used. They were housed in groups of two or three cats in enriched cages with access to an outdoor part during daytime. Due to body condition at the age of eight month the cats were divided into two groups of a lean (l) and of an obese (o) phenotype. A genetic background of the phenotypes could be proofed (Häring et al., 2011). All cats had a Body Condition Score (BCS) of 5 to 5.5 out of a scale of 9 at beginning of the measurements. In this study three different experimental diets as defined before were tested: HCH, HF and HP. The study was divided into two trials. In both trials the day before the feeding period started, a blood sample was taken. In trial A, each diet was fed for 7 days and at day 8 blood sampling was performed before the meal (0), and 15, 30, 45, 60, 120, 180 and 240 min after the meal. In trial B each diet was fed for 3 weeks, than the same blood sampling schedule was performed with an additional blood sampling 24 hours after the meal. For blood collection the cats were sedated with propofol. BCS was assessed at the beginning and the end of each feeding period. Blood samples were analysed for glucose, insulin, leptin, triglycerides and free fatty acids (FFA). Data are given as mean and standard error (SE). Significant differences (p<0.05) were tested by ANOVA and correlated influences were tested by regression analyses with help of SPSS®
Results: There were no differences between the two phenotype groups in glucose, leptin and free fatty acids, but insulin and triglyceride values were significantly correlated to phenotype (p<0.05). Blood triglyceride, leptin and insulin values were connected significantly to the trial and diet (p<0.05), FFA to diet (p<0.05) and insulin was also depending on time after meal (p<0.01). The insulin blood values showed a higher increase after feeding in the genetically lean phenotype. Especially during feeding the HCH diet, insulin values of the cats of group l were higher in group 1 compared to group o.
Discussion: The present data show a different reaction of the normal lean cats compared to the cats predisposed to obesity. The insulin data indicate that for the cats predisposed to overweight, avoiding a high carbohydrate feeding over long time would be beneficial for their health. Nevertheless, the measured glucose values show that all cats were able to keep glucose in a normal range independent to diet, at least at their present age. This may also be true in humans.


BEHAVIOURAL MODEL OF FOOD ADDICTION IN MICE
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An increasing perspective conceptualizes obesity and overeating as disorders related to addictive processes that are associated with specific brain changes. Certain commonalities exist between eating and drug use, such as mood alteration, external cue-control of appetite or motivation for reinforcement. Addiction is a chronic brain disorder characterized by an impaired ability to regulate the drive to obtain and use the drug, in addition to the onset of relapse. At present, it is discussed whether or not specific food eating disorders should be viewed as addictive processes. To explore the behavioural hallmarks and the neurobiological basis of food-addiction, it is essential to validate a reliable animal model of addictive-like behaviour to palatable food. Recently an animal model of drug-addiction has been developed in rats, based on the DSM-IV criteria of substance dependence. In the present study, an animal model of food addictive-like behaviour was validated in mice under operant conditioning, maintained by chocolate-flavoured pellets. Persistence of food seeking during a period of signalled no availability of food, motivation for drug seeking and perseverance of the mouse’s responding when the reward was associated with a punishment were evaluated. This model was used with the purpose of identifying two different and extreme populations of mice related to addiction score: addict population from non-addict population. We investigated the epigenetic changes in these two different populations. DNA methylation at CBR1 and CBR2 gene promoters were analyzed by real-time methylation-specific PCR. Preliminary results revealed that DNA methylation of CBR1 gene promoter region was different between addict and non-addict animals in prefrontal cortex and nucleus accumbens. Indeed, addicted mice trained with chocolate-flavoured pellets showed decreased DNA methylation of CBR1 gene promoter, which could correspond to a gene up-regulation expression of CBR1 receptor in prefrontal cortex. Furthermore, a significant down-regulation of CBR1 gene expression in the nucleus accumbens with a consistent increase in DNA methylation at gene promoter region of CBR1 receptor was observed. Furthermore, no significant differences were observed for DNA methylation at CBR2 gene promoters in prefrontal cortex and striatum. This study provides new evidence for a better understanding of the neurobiological mechanisms that may lead to addictive-like behaviour related to food intake.
Day 3: Anti-Obesity Drug Discovery and Development

Invited Speakers Abstracts

Pharmacotherapy for obesity: limited options but plenty of ideas
Professor Jon Arch, Dean of Science, Medicine & Dentistry, University of Buckingham
Professorial Research Fellow and Deputy Director of Metabolic Research, Clore Laboratory, Buckingham Institute of Translational Medicine, University of Buckingham, UK

Almost the only drug available for the treatment of obesity outside the US and Japan is the pancreatic lipase inhibitor orlistat, which is little-used. In the US the old amphetamine-like drug phentermine is by far the most prescribed drug. Phentermine combined with topiramate, and lorcaserin have been approved but sales have been poor and they have not been approved by the EMA. NDAs have been filed for liraglutide. Niche obesity markets may allay safety fears. Brown adipose tissue appears to offer many drug targets, but drugs will have to improve upon past or cheaper approaches to its activation.

Molecular Characterization of White and Brown Adipocytes Reveals Complex Phenotypes
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Introduction: Over the last two decades the prevalence of obesity has reached epidemic levels not only in highly industrial countries but also worldwide. Secondary major health risks, such as hypertension, insulin resistance, type 2 diabetes and cardiovascular diseases, can be summarized as the metabolic syndrome and are highly associated with obesity. In cases in which energy intake e.g. through high caloric food intake exceeds energy expenditure the overall energy homeostasis is imbalanced. This excess energy is stored in the body in form of white fat, which eventually results in obesity. White adipose tissue (WAT) depots therefore, mainly act as the body’s main energy storage and additionally act as an endocrine organ by releasing adipokines and cytokines into the body. Additionally, functional brown adipose tissue (BAT) has recently been discovered through radiological detection by several research groups in the last years in substantial amount in adults. Formerly overlooked BAT, which was thought to be absent in the human adult, has therefore recently become an interesting anti-obesity target due to its ability to dissipate energy in form of heat.

Methods: We cultured and extensively characterized human brown PAZ6 adipocytes in comparison with a white adipose cell line SW872. In addition, human SGBS adipocytes were included in the analysis. Brown and white adipocyte markers were tested by quantitative Real-time PCR. Fluorescent and Oil-Red staining assessed the quantity and quality of the differentiation process. Next generation RNA sequencing of undifferentiated and mature SGBS and PAZ6 cells was performed in order to elucidate pathways distinctly activated in white vs. brown human adipocytes. Functional assessment of oxidative rates of each cell line was conducted using the Seahorse technology.
**Results:** Whereas PAZ6 and SW872 cells showed classical molecular and phenotypic markers of brown and white adipocytes, respectively, SGBS cells presented a versatile phenotype of adipocyte. 14 days after initiating the differentiation process the expression of classical brown marker such as UCP-1 and PPARg peaked and declined until day 28. The white adipocyte marker Tcf21 however, showed reciprocal behavior. Interestingly, Leptin levels peaked at day 28 whereas the highest adiponectin mRNA levels were monitored at day 14. Phenotypic analysis of the abundance and shape of lipid droplets were consistent with the molecular patterns. On day 14, SGBS cells showed multiple small droplets, however the number of droplets decreased and the size increased until day 28 as expected for a white adipocyte phenotype. Lastly, functional metabolic analysis showed the highest oxidative rate of mature SGBS cells on Day 14, which remained consistent or slightly decreased until day 28.

**Conclusion:** SGBS cells are widely used as a model for white adipocytes. Our data suggest that the cell line harbors a versatile phenotype, which changes throughout their mature stage. Day 14 displays multiple characteristics of brown fat cells such as UCP-1 overexpression whereas day 28 is representing a rather white phenotype. Many reports suggest recently that the traditional classification of adipocytes is not exclusive and the existence of beige/brite adipocytes has been shown. We are presenting data derived from a human cell line model, which harbors characteristics of both distinct phenotypes. This unique situation allows the study of molecular switches and pathways involved in the conversion between white and brown adipocytes. This knowledge will be of importance for studies aimed to increase brown fat depots in order to increase energy expenditure in obese subjects with the ultimate goal of weight reduction.

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**Galanin-like peptide (GALP) have anti-obesity effect via the activation of hepatic lipid metabolism**

*Dr Satoshi Hirako*, Post-doctoral fellow, Dept of Anatomy, Showa University School of Medicine, Tokyo, Japan

Galanin-like peptide (GALP) is produced in neurons in the hypothalamic arcuate nucleus and is well known as a neuropeptide regulating feeding behavior and energy metabolism. In this study anti-obesity effect was obtained by the 7-day intranasal administration of GALP in obese mice. The respiratory exchange ratio (RER) of GALP group was lower than the saline group. In addition, fatty acid oxidation-related gene mRNA levels were increased in liver by administration of GALP. The present study indicates that anti-obese effect of GALP may be caused by anorexigenic effect and improvement of lipid metabolism in the liver.

**Thiol redox state as a novel pharmacologic target for obesity**

*Dr Amany Elshorbagy*, Visting Postdoctoral Research Fellow, Lecturer in Medical Physiology, University of Oxford, UK Universityi of Alexandria, Egypt

Mouse knockouts of several enzymes in the sulfur amino acid pathway are characterized by increased energy expenditure and resistance to diet-induced obesity. Common to these models is decreased cysteine synthesis and/or plasma total cysteine, and profound hepatic suppression of the key lipogenic enzyme stearoyl-coenzyme A desaturase-1. This talk will include our latest data on using thiol-modifying drugs in mice to control fat mass. Pilot studies using 2 such drugs have shown promising results. The concept is novel, and builds on epidemiologic work showing that plasma total concentration of the thiol amino acid cysteine is one of the strongest parameters associated with fat mass in humans.

**Antipsychotics induced obesity: Direct actions on the adipocytes**

*Professor Nira Ben-Jonathan*, Professor of Cancer and Cell Biology, University of Cincinnati, United States

Atypical antipsychotics (AAP) are prescribed to millions of patients with mental diseases. Although AAP ameliorate mental dysfunctions, they have serious metabolic side-effects such as weight gain, diabetes, and cardiovascular disease. We discovered expression of functional dopamine and serotonin receptors in human adipocytes and found that AAP altered many of their functions. We propose that direct actions of AAP on adipose tissue contribute to weight gain and the metabolic syndrome. Human
adipocytes could be integrated into the screening paradigm of candidate new drugs for the identification of undesirable metabolic activities prior to costly animal studies and clinical trials.

**Hypothalamic proopiomelanocortin (POMC) down regulation after weaning is associated with hyperphagia-induced obesity in JCR rats over-expressing neuropeptide Y**

Dr Abdoulaye Diané, University of Alberta, Edmonton, Alberta, Canada

**Poster Presentations**

**CLINICO-ECONOMIC ANALISIS OF METABOLIC SYNDROME’S TREATMENT.**

I.M. Sechenov’s First Moscow State Medical University, Russia.

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**Objective:** To compare efficacy of the two schemes of treatment of metabolic syndrome (MS): lifestyle modification and the complex therapy (lifestyle modification + orlistat + metformin) based on results of pharmacoeconomic analysis.

**Methods:** A total of 60 patients with MS was included in the study. The study group (30 subjects mean age 41,0±11 years, women - 23 (76.7%)) received the complex therapy of MS – lifestyle modification, orlistat 120 mg x 3 t./day and metformin 850 mg x 2 t./day. Control group (30 patients mean age 43,4±9.5 years, women - 26 (86.7%)) was treated with lifestyle modification. At the stage of inclusion in the study and after 6 months of therapy all patients underwent clinical and laboratory investigation and assessment quality of life (QL) according to the SF-36 questionnaire. We constructed a multi-state life-table based Markov model in Excel in which presents of MS influences the incidence of stroke, myocardial infarction (MI), type 2 diabetes mellitus (DM-2) and death. Risk reduction in the control group based on the data of clinical trials that modest weight loss would be lower risk of type 2 DM, but not affect risks of MI and stroke. Risk reduction in study group based on data of clinical trials that weight loss ≥10% and blood pressure ≥12/8 mm hg will reduce both the risk of DM-2, MI and stroke.

We use data on risks of MI, stroke and DM-2 identified from PubMed searches, on disease costs from the Russian pharmacoeconomic researches, and on drug costs from the average cost for Moscow and Department of Health. We use a lifetime horizon for costs and health outcomes. Health effects measured as QALYs and costs in Euro, discounted 5%. To assess the dependence of the results of input parameters we conducted sensitivity analysis. To assess the value of 1 QALY used willingness to pay ratio (wtR), equal to three times the size of GDP. Based on wtR, QALY and direct costs was calculated NMB (net monetary benefit) for each therapy.

**Results:** We received more significant improvement of all clinical outcomes (body weight and blood pressure, glucose and fat metabolism indices) and QL in study group compared with the control. The simulation results showed that the complex therapy of MS allows increasing the average life expectancy for 2,3 years and prevents 4 death, 3 cases of MI, 1 stroke and 8 new cases of DM-2 in a group of 100 patients for 20 years. The standard treatment of MS allows increasing the average life expectancy for 0,7 years and prevents 1 death, 2 cases of MI, 0 stroke and 4 new cases of DM-2 in a group of 100 patients for 20 years. NNT for complex therapy is 6.3, for standard treatment – 16.7. QALY for complex therapy is 9.45, for standard treatment – 8.63. The cost-utility analysis showed that cost per 1 QALY is €1284 (1220 € discounted) for standard therapy and 1077 € (1023 € discounted) for complex treatment of MS. wtR for Russian Federation is 29 071 €. NMB is €239 798 (€240 352 € discounted) for standard therapy and €264 544 € (€265 053 € discounted) for complex therapy of MS. Depending of input parameters. Sensitivity analysis showed that regardless of the input parameters, complex therapy of MS will be a priority.

**Conclusions:** It is shown that the complex therapy of MS, including pharmacotherapy of obesity and insulin resistance is a priority compared with standard therapy, as characterized by the best results of NNT, LYG, QALY, CUR and NMB.