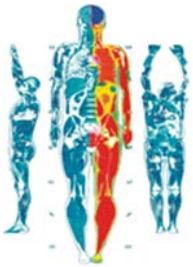


MRC Neuroscience of Obesity Workshop: Gut – Brain Communication

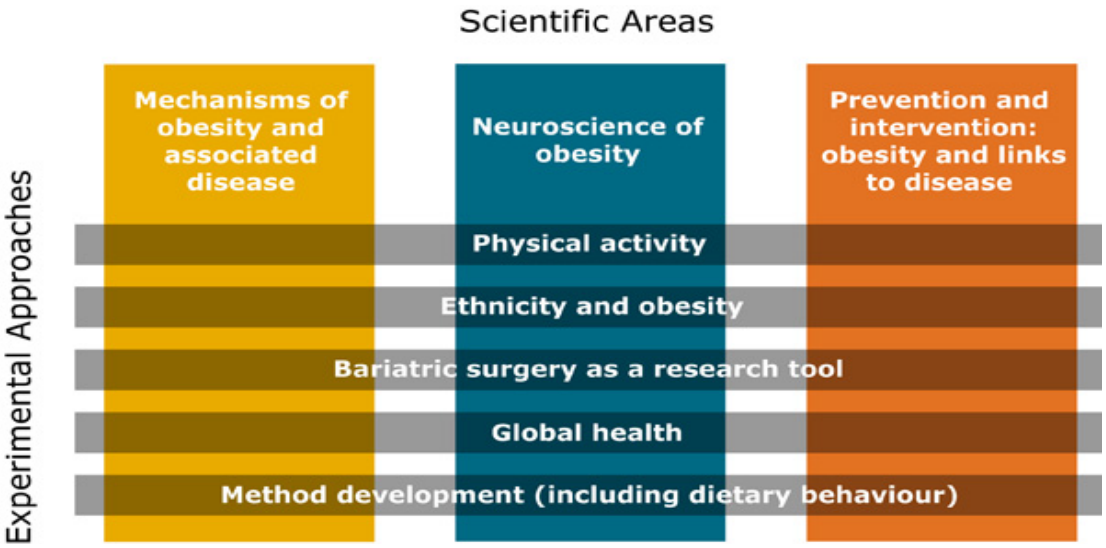
REPORT OF THE WORKSHOP HELD ON 9 & 10 OCTOBER 2014

Background and meeting objectives

The meeting was hosted by the MRC Metabolic Diseases Unit (MDU) and held under the aegis of two MRC Research Boards - the Population and Systems Medicine Board (PSMB) and the Neuroscience and Metal Health Board (NMHB).

Obesity and its related diseases place a significant burden on healthcare systems and tackling obesity is a government-wide priority in the UK. Within the MRC's broad remit, a significant amount of research relevant to obesity and obesity-related disease is funded. In 2013/14, the MRC spent over £23 million on research relevant to obesity through research grants and to its units, centres and fellowships. Further information on the MRC's activities in relation to obesity and the microbiome can be found via the links provided.

In 2010 the MRC held a meeting of leading obesity researchers to produce a coherent set of priorities for MRC obesity research, taking into account current activities, opportunities, tractability and clinical relevance. Eight priorities for MRC obesity research were identified and divided into two categories: scientific areas and experimental and conceptual approaches. Some research priorities were considered to be areas of strength for UK research where significant progress was being made, whereas others were viewed as under-developed and in need of stimulation.



Aims of the Workshop

The aim was to hold a small and highly interactive workshop focused on the neuroscience of obesity, and gut-brain communication in particular. Both PSMB and NMHB had previously identified this as an important area where the MRC portfolio should be strengthened.

Four planned sessions covered:

i) Gut/brain communication, including how bariatric surgery exerts its physiological effects
ii) Neuronal mechanisms of energy homeostasis - hypothalamus/brainstem
iii) Hedonic, behaviour, addiction and higher cognitive function, including brain imaging
iv) Novel therapies and drug targets

The agenda and list of participants for the workshop can be found at Annexes 1 & 2.

The workshop drew together experts from across the spectrum of research with the aim of considering how the field had evolved since the MRC developed its obesity priorities in 2010, and identifying priority topics through which the MRC could make an impact.

The overall aim was to shape the future strategy for the MRC in this field by:

- Highlighting the UK's strengths
- Discussing barriers to progression
- Identifying and prioritising key interdisciplinary research challenges and translation opportunities relevant to this field
- Bringing together a broad spectrum of scientists and clinicians with relevant expertise
- Facilitating collaborative and interdisciplinary interactions and encouraging high quality, multidisciplinary grant applications from the scientific community

Format of the meeting

The workshop took the form of a short retreat to encourage wide-ranging discussion and creative thinking around the area. The workshop began early evening on the 9th October with short briefing presentations from Professor Hugh Perry and Professor Sir Stephen O'Rahilly, followed by dinner. On the following day each of the four sessions were led by two key experts with the aim of stimulating whole group discussions on each topic. Short biographies of the speakers and session leads can be found at Annex 3.

The following key questions were used to guide each discussion session:

- Where is the field now? (UK strengths and weaknesses with respect to research/ infrastructure/technology)
- Where should the field be heading?
- What are the priority research gaps?
- What questions should be addressed to improve our understanding of the field?
- What are the key barriers to collaboration/joint working across disciplines on these questions. How can these be overcome?
- What are the potential translational gains/opportunities and what is needed to achieve them?

Discussions were centred around:

1. The here and now –e.g. what 'quick wins' might be addressed.
2. Short/medium term challenges – e.g. progress with any therapies currently being tested, hot topics in translational research and what might be 'in the pipeline' for improvement.

3. Long term prospects – e.g. outcomes resulting from an increased understanding of the biology and how this might shape future scientific and clinical direction in the field.

Pre-Workshop Survey

Prior to attending the workshop, participants were asked to complete a short survey to identify:

i) Two priority research gaps which, if addressed, would improve our understanding of this field
ii) Two key issues/areas which, if addressed, would enable progression in the field

The participant responses were included in the workshop papers and collated without attribution (Annex 4). These responses were used to inform the direction of the discussions in the four sessions on day 2.

Workshop Report

Session 1: Gut/brain communication, including how bariatric surgery works

Session Leads: Fiona Gribble & Carel Le Roux

A brief introduction by the session leads highlighted the importance of this particular area of obesity research. GLP-1-based medicines are already a multi-billion pound industry for Type 2 Diabetes and gut peptides are also currently under development for the treatment of obesity. Furthermore, bariatric surgery is highly effective and results in dramatic and sustainable weight loss. Based on the pre-workshop survey responses, four key areas for discussion were identified:

- Gut microbiota
- Enteric nervous system and signalling between gut and brain
- Bariatric surgery
- Gut hormones

Gut microbiota
A number of workshop attendees felt that this was an important area of research, where there are currently gaps. A good deal of effort in this area was from outside the UK. The key points raised during the discussion were:

- Despite experimental evidence that the microbiome can play a causal role under experimental conditions in rodent models, its role in the development of obesity in humans is still unclear and causality remains to be addressed. Whilst large-scale studies may provide evidence of correlations between microbiome composition and human obesity, the demonstration of causality in humans requires interventions that both perturb the gut microbiota and modulate obesity.

- It may not be necessary, and it may in fact impede progress, to take a reductionist approach and study individual populations of gut bacteria. Gut microbiota exhibit regional heterogeneity - stool samples are not useful because they do not reflect populations higher up the gastrointestinal tract. Efforts should be focused on understanding the overall function(s) of the gut microbiota as a community and how functions vary across different human populations. Current understanding in this area is very limited.

- The main research gap, for which there was considerable support and which could become a UK strength, is the “black box” of communication between gut microbiota and brain. This was highlighted as an important area where basic scientific efforts are

needed. Work is required to identify and characterise the plethora of signals, going beyond short chain fatty acids, and the signalling routes underlying gut bacteria – host communication.

- There is also a gap in understanding of the local effects of the gut microbiota on barrier function and inflammation.

- The large intestine was very important in harvesting energy from ancestral diets. It was argued that it would be interesting to recreate these dietary conditions and determine effects on energy balance in humans.

- Studying the metabolism and energy balance of colectomy patients, with significant alterations in their gut microbiota, could be a critical experiment.

- There was support for the utility of both human studies and mouse models in this area. The impact of the microbiome on obesity and on insulin sensitivity should be separated out.

Enteric nervous system and signalling between gut and brain

The key points raised during the discussion were:

- The enteric nervous system (ENS) has been shown to express receptors for gut hormones. However, how the ENS interacts with the gut-brain axis and the importance of the ENS in appetite regulation are largely unknown. The development of tools, such as transgenic mice, to address these gaps would be valuable.

- There are tools available which would allow progress in this field, such as viral gene delivery techniques enabling the targeting of subsets of neurons. However, it was felt that the UK has been left behind in this area.

- Little is known regarding the ENS in obese humans and this is an important gap. Do ENS disorders affect metabolism/physiology and are effects direct or indirect? Work is currently dominated by rodent studies. However, it was argued that human pathology is complex and therefore, animal models remain important.

- The metabolic role of the autonomic nervous system is ill-defined. Work should focus on the link between metabolic diseases and autonomic neuropathy. The autonomic nervous system may play a role in the development of obesity-associated co-morbidities.

Bariatric surgery

Bariatric surgery has profound effects on body weight and metabolism, and changes individuals' attitude to food entirely. It is a very important tool which can provide valuable insight, however, we are a long way from understanding how it works. The UK has a strong track-record and is recognised internationally as a pioneer in this field of research, particularly with regard to rodent models of bariatric surgery. This reputation has also attracted principal investigators from abroad. The key points raised during the discussion were:

- The mechanisms underlying the dramatic beneficial effects of bariatric surgery remain incompletely understood. This was identified by the MRC workshop attendees as a key priority for obesity research. The relative contributions and interactions of different systems such as the enteroendocrine system, the nervous system and the gut microbiome following bariatric surgery require further investigation. The ultimate goal would be to mimic the effects of bariatric surgery pharmacologically.

- It is important to distinguish between the effects of bariatric surgery *per se* versus the effects of body weight loss and severe caloric restriction alone.

- Transplantation of gut microbiota from different parts of the post-surgery gut into germ-free mice may be an interesting experiment.

- A question raised was how many bariatric procedures should be studied in rodent models? It was argued that depth was better than breadth and that the focus should be on the main procedures carried out in humans, namely sleeve gastrectomy and Roux-en-Y gastric bypass (these account for 60% of total procedures).

- Bariatric surgery research would greatly benefit from workshops and training centres/programmes on animal models/procedures. This was identified as an important gap and received considerable support from the MRC workshop attendees.

- It is important for human studies to be conducted alongside rodent studies. Rodent models of bariatric surgery closely mimic effects in humans.

- Could we learn from non-responders? They are a heterogeneous group of patients and a big cohort would be required to distinguish them. However, information gleaned from such studies could be interesting.

- Understanding the effects of bariatric surgery in humans would be facilitated by a cross-disciplinary approach, combining the efforts of human feeding behaviour scientists, peptide biologists and clinicians.

- Functional imaging in humans is a powerful tool and should be coupled with bariatric surgery.

- Medical devices have thus far not been very effective. Efforts in this area are mainly from the US. This area could profit from engagement with industry.

Gut hormones

The importance of gut hormones, both physiologically and as drug targets, is well-recognised. Furthermore, this is an area of research where the UK has world-leading expertise. The main points raised during the discussion were:

- Gut hormones can act via multiple mechanisms and there is a tendency to investigate pharmacological doses/effects. Physiologically, the effects of individual gut hormones are likely to be modest but amplified when in combination. However, it is difficult to design experiments to unpick this complexity and determine optimal gut hormone levels/profiles. It is important to prove their physiological relevance and elucidate the pathways responsible for their effects.

- Clarification is required regarding the role of gut hormones locally in the gastrointestinal tract versus centrally to modulate appetite. It was proposed that we should capitalise on new techniques to discriminate between the action of peptides in the gut and the brain. The hedonic role of gut hormones, beyond hunger and fullness, is also incompletely understood.

- Food/nutrients have potential for the prevention of obesity. Work should focus on functional foods which increase gut hormone secretion more effectively and have enhanced satiety properties. This was deemed to be an important strategic gap.

- Improved understanding of the differences along the gastrointestinal tract and which regions underlie plasma gut hormone profiles would help to identify which pool of enteroendocrine cells should be targeted.

Session 2: Neuronal mechanisms of energy homeostasis - hypothalamus/ brainstem

Session Leads: Giles Yeo & Julian Mercer

Genetic approaches have almost exclusively directed obesity research to the brain, and in particular the hypothalamus. Moreover, many obesity pharmacotherapies target the brain to promote negative energy balance. The neuronal mechanisms of energy homeostasis therefore represent a critical focus for basic and translational research in the field of obesity research. Based on the pre-workshop survey responses, four key areas for discussion were identified:

- Hypothalamus
- Hindbrain
- Signal in and integration of cues from the periphery
- Onward signalling and crosstalk

The session began by considering the question: *What are our strengths as a neuroscience community in the UK, and what are the opportunities and potential barriers?* The key points raised during the discussion were:

- UK strengths include classical neurophysiology and the identification of function.

- Mouse genetics is a UK strength which offers a number of opportunities. The UK possesses the expertise and infrastructure to make mouse models on a considerable scale. In addition, participants emphasised that there are many more GWAS hits to investigate.

- Whilst UK scientists were quick to apply new technology (not just genetic engineering) to metabolic disease, the UK was lagging behind other countries in relation to the development of new methods. There is a need to invest substantial funding into progressing technology and to ensure that UK neuroscience centres of excellence place an emphasis on developing technology, with engineers and computer scientists working alongside neuroscientists.

- There is a need to ensure the UK was at the forefront in understanding how brain circuits process information to create neural representations that guide behaviour. It was recognised that this would require multidisciplinary approaches linking cutting-edge genetic tools and other new technologies to enable classical neurophysiology to be applied in a smarter, more targeted way.

- It was noted that the UK Brain Banks Network provides high quality brain tissue to scientists and clinicians to carry out cutting edge neurosciences research. The members of the Network will also explore the scope for greater specialisation of some brain banks to address particular research needs. Participants discussed the possibility of capitalising on the collection by linking samples to appropriate clinical data (e.g. Body Mass Index - BMI).

- As a weakness of UK neuroscience research, the legislative framework from the Home Office is a short-term barrier that needs to be addressed. It was suggested that it would be impossible to recreate John O'Keefe's Nobel-prize winning research with same speed and ease today. Closer working between the Home Office and scientists to explore new approaches could be implemented. Submitting reports on new experimental approaches with small numbers of animals, in the first instance, would ensure confidence in the cost-benefit relationship.

In light of the unexplored GWAS hits, the session then turned to addressing the question: *Should we concentrate on what we know or invest in finding new neural contributors to the neuroscience of obesity?* The key points raised during the discussion were:

- There was a need to study existing mouse models in much more detail – this was particularly important when looking for potential drug targets.
- Even though pro-opiomelanocortin (POMC) and the melanocortin 4 receptor (MC4R) are well studied, not enough is known about important components upstream of these key mediators e.g. nutrition, movement/physical activity, fat cell products.
- There are areas where overseas groups have a strong lead - for example the work of Scott Sternson and Brad Lowell in relation to Agouti-related peptide (AgRP) – and it may be better for UK researchers to focus on areas where they can develop novel insights.
- Participants agreed that key leads may be missed by focusing on one system - there was a need to take a more holistic view of the problem and examine both established and new players regulating appetite and their possible interactions.
- Much research had focused on the homoeostatic regulatory system in the hypothalamus and dysregulation leading to obesity. It was agreed that it would be productive to look for higher level changes e.g. in relation to seasonality and synaptic plasticity. Digression from an ideal bodyweight would simply represent physiological flexibility/adaptation to particular circumstances.

The following key points emerged from a discussion on the role of imaging:

- The ability of brain imaging to spatially and temporally locate brain areas involved in processing metabolic cues was emphasised.
- One limitation is the language of interpretation around brain imaging. Can we better develop a cogent neuroscientific vocabulary for interpreting brain imaging and relating it to physiology and mechanisms? How do we best link changes at the single cell level, to fMRI scans and physiology, through to behavioural change?
- It was suggested that the UK community needs to better utilise small animal brain scanning and also to capitalise fully on the recent significant investment in human imaging (including 7T) that had been made through the Clinical Research Infrastructure Initiative. The challenges of accommodating obese patients in scanners were highlighted.

The focus of the session then moved to the hindbrain and the following points were made:

- Much of our research in the neuroscience of obesity is focused on the hypothalamus but brain sites sensing metabolic cues may be distributed throughout the brain. In fact, many key conduits located in the hypothalamus are also expressed in the brainstem. A key question that was highlighted was to understand whether these distributed sites may be redundant circuits.
- Hindbrain systems are known to control both energy balance and cardiovascular disease. In this regard, the treatment of obesity via increased energy expenditure may be held back by side-effects on the cardiovascular system. It was suggested that the hindbrain may play a role in this via autonomic output.

Finally, participants discussed the importance of the 'connectome':

- It was important to recognise that the system under study is a neurocircuit and it is likely that neural sites interact - one site cannot be studied in isolation.

- The Allen Mouse and Human Brain Atlases were invaluable resources for neuroscientists. The Allen Mouse Brain Connectivity map provided brain-wide, cellular level mesoscale connectome information. The Human Connectome Project will map connections between brain regions whilst the human Brain Initiative will look at connectivity between small clusters of neurons.

- There is a need for an integrated framework for metabolic function and food intake, linking brain connectivity with functionality – a 'functional connectome' which shows the generation and processing of key signals, how they are routed, combined and co-ordinated, leading to behavioural and physiological outcomes. In addition, it is important to understand the flexibility/adaptability of the system in relation to external influences (e.g. quantity and type of food available). For this reason experts in metabolic function and obesity should work with neuroscientists to produce a common neural map which researchers could update as they publish.

Session 3: Hedonic, behaviour, addiction and higher cognitive function, including brain imaging

Session Leads: Paul Fletcher & Sadaf Farooqi

The session discussion acknowledged the complexity of eating behaviour and challenges inherent in studying and understanding it. Eating behaviour is driven and modified by multiple factors: hunger, metabolic requirement (basal and energy expenditure), early life programming, the environment (physical and social) and beliefs (cultural and individual). Given these multiple interacting factors it is difficult to determine what drives food related decisions and food consumption on a day-to-day basis. BMI serves as a cumulative record of these decisions but in itself only tells us that there has been excess energy intake surplus to requirements, not how or why. The issue is rendered more complex by the fact that most of our food related decisions are habitual and driven by environmental factors, rather than deliberated or goal directed. For example, the clock that tells you it is 1:00pm is an extremely important environmental signal that motivates eating lunch.

This can be understood in our conceptualisation of the brain as a predictive organ, one that aims to constantly model our environment (both internal and external), predicts changes in the environment and efficiently implements appropriate responses to it. In this conceptualisation, the brain strives to make predictions and optimise behaviours such that they can be implemented as efficiently as possible (habitually), minimising the need for energetically expensive deliberation. A striking illustration of this predictive model is shown by the anticipatory rise in ghrelin levels when people believe they are about to have an indulgent creamy milkshake compared to a healthy one, even though both drinks are identical apart from their labels. However there are two important consequences of this striving for efficiency. The first is that actions/behaviours become dissociated from the value of their outcome. Habitual behaviours remain unaffected by changes in the value of the outcomes they result in and continue to be activated by environmental cues, even though their outcomes are no longer valued or now potentially harmful (e.g. continued consumption despite obesity). The second consequence is that the outcome, or the reward, also becomes dissociated from its value, as it results from a habitual behaviour that does not factor in its value, or how it may have changed since the last time it was encountered. Computational neuroscience approaches can help us study and understand eating behaviour and help us examine critical questions such as: Is the brain aware of existing adiposity stores when it makes food related decisions?

In addition to the above, participants discussed the following specific areas:

- *The need for more precise measurement tools for characterising obesity relevant phenotypes:*

    - *Quantification of eating behaviour phenotypes:*
      This is a major challenge, as accurately measuring food intake remains a significant hurdle in this area. Most present tools rely on self-report or some form of active subject participation in the measurement. Recent advances have included using body mounted cameras to capture images of foods eaten, chewing rate and purchasing behaviour, and developing the sophistication to extract precise data on the eating behaviour from these outputs alone, e.g. determining portion size and calorie content from a photo of a meal. Critical to these tools is the ability to accurately measure behaviour without the process of measurement significantly modifying the behaviour itself. It was agreed that this is an important area of future research.

    - *Quantification of energy expenditure and physical activity:*
      In this area there has been significant progress in the development of sensewear technology that can accurately and unobtrusively measure activity. It is important to integrate this with the eating behaviour phenotype given the coupling of energy intake and expenditure and the role that energy expenditure plays in both determining intake as well as its effects on appetite control.

- *The effect of our present day environment on eating behaviour and body weight:*
  There have been significant changes in our food environment (particularly over the last few decades) compared to the environment we evolved in, and these have had an effect on food intake and body weight. Changing the food environment is an important part of any anti-obesity strategy. However, this altered environment also poses some important questions such as: How do individuals maintain a healthy body weight in this environment? What factors drive thinness?

- *The challenges of selectively targeting food reward to treat overeating and obesity:*
  Food reward has been an important therapeutic target in recent years, with cannabinoid and opioid agents that have aimed at reducing food reward and therefore intake and weight. However, a challenge with these drugs has been that their effects have not been limited to food rewards and achieving this degree of specificity remains an important gap.

- *The potential value of examining other conditions in which eating behaviour and weight are affected:*
  Studying these conditions can help improve our understanding of the drivers of intake. These include: anorexia nervosa, cancer cachexia, post-operative cachexia, inflammation, drug induced obesity (antipsychotics, antiepileptics), frontotemporal dementia, Huntington's disease and hypoxia related changes in appetite.

- *The food addiction model:*
  This has gained a lot of currency particularly in the USA, where it has strong proponents, and on the Internet. While there is compelling animal evidence to suggest that addiction type behaviours can be induced in animal models, there is no evidence thus far to suggest that any foods act like drugs. More recently the idea of an eating addiction, rather than a food addiction has been raised, suggesting that it is the behaviour that is the issue and that a potential substance is not involved. It is very unlikely that addictive processes underlie most of obesity but they may be relevant to specific phenotypes and this requires further research.

Session 4: Novel therapies and drug targets

Session Leads: Stephen Bloom & Lora Heisler

There is a critical need for better treatment of obesity: current pharmacological anti-obesity treatment is only moderately effective (leading to 5% of weight reduction at the most) at the expense of many off-target side-effects. In addition, although bariatric surgery is effective in many, it has some significant down-sides: some patients do not respond with weight loss, it bears the usual complications associated with major surgery, and finally not many are keen to have a major operation.

Professors Bloom and Heisler presented a short introduction to the session covering past and present drugs that have been used to treat obesity and the potential targets for effective drug treatment of obesity (e.g. central and peripheral regulation of food intake, energy expenditure, physical activity, fat absorption and metabolism). Two important advances in the field had occurred: the drug companies are now much more open to peptide drugs largely delivered by injections, and insurance companies are now reimbursing treatment with anti-obesity drugs.

The UK has the potential to be a global leader in the development of drugs by virtue of the clinical infrastructure provided by the NHS (including data linkage) and available funding schemes to support drug discovery research.

Participants discussed the potential quick wins in drug development, the short and medium term developments (which drugs are in the pipeline?) and the future for anti-obesity therapy. The following key points were made:

- Low dose combinations of existing drugs (e.g. 5-HT_{2C} receptor agonist with gut peptides) offer a quick win as they are available and could enter trials of efficacy in a relatively short period of time. Also, combination of various gut peptides have been proven to induce weight loss in rodents and an MRC-funded phase I trial in humans is imminent.

- Targeting of drugs to specific relevant tissues through manipulation such as ligation offered an additional approach of improving efficacy and limiting off-target effects.

- Another potential avenue to increase the efficacy of existing drugs is to study their mechanisms of action at the behavioural level e.g. lorcaserin: Does it increase satiety response or decrease reward of food or both? This knowledge can then be used for behavioural therapy to potentially enhance the effects.

- The following were discussed in relation to medium and longer-term goals:

  Understanding the effects of bariatric surgery – specifically to pharmacologically mimic the beneficial effects of surgery through understanding the postoperative gut hormone dynamics and the effects on appetite.

  Nutraceuticals - manipulating food to increase the hormonal gut satiety response. Proof of concept studies would need to take place first to establish whether it was possible to deliver sufficient functional nutrients to the right place in the gut and whether the gut hormone response would be powerful enough to control food intake in a sustained way.

- Areas that were explored as potential targets for obesity treatment were drug interventions aimed at increasing energy expenditure, browning of fat, inducing physical activity, or inducing malabsorption; none of which seemed attractive as primary targets of anti-obesity treatment as they have the potential to result in compensatory effects on food intake.

- Exploring the properties of the microbiome in relation to obesity treatment was discussed. However, as noted above, a lack of robust evidence linking the microbiome to causality of obesity was identified as a barrier to this approach.

- Another potential avenue to be explored was the manipulation of food to make it non-absorbable, or increasing gastric/gut transit time to allow more release of anorexigenic gut hormones.

Future strategies

The future for anti-obesity treatment was discussed: drugs, lifestyle or surgery? In general it was agreed that a combined approach would be the way forward.

Agreement was also reached that pharmocogenomics and other approaches should be used to stratify responders vs. non-responders to specific pharmacological manipulation, and to identify those who are more or less likely to experience side-effects.

Increased partnership with industry who, often by virtue of regulation, have collected large datasets, was recommended as a way forward to data mine and collectively identify better and cleaner drug targets for anti-obesity treatment.

Finally, it was widely agreed that the drugs that are currently used are associated with too simplistic an understanding of the neuro- and gut-circuitry of body weight control. Basic scientific studies and genetic studies need to be encouraged to refine treatment targets. For this we need adequate capacity in obesity research in the UK.

Report written co-ordinated by Karen Finney with contributions from:
Arianna Psichas (session 1), Luke Burke (session 2), Hisham Ziauddeen (session 3), Agatha van der Klaauw (session 4).