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VIEWS

Organ cross-talk and the aetiology of obesity – an impasse.

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Obesity is a chronic health condition that has become a global catastrophe because it is a predisposing factor for many non-communicable diseases such as type 2 diabetes, hypertension and other cardiovascular diseases and cancer. It is clear that obesity is a problem of energy imbalance, and that the primary underlying cause is an excess of food intake relative to the amount of energy being expended[1]. However, while this explanation must be correct, as it is based on the laws of thermodynamics, it is not particularly useful, because it tells us nothing about what causes that imbalance in the first place. Moreover, this viewpoint leads to a rather simplistic approach that all we need to do then to reverse the obesity epidemic is to tell people to eat less and move more, and that will place them into negative energy balance and they will lose weight. That approach, however, assumes that these parameters are under conscious and voluntary control. The systematic failure of every government that has adopted this eat less, move more strategy to try and tackle the obesity problem is a clear signal that they are not, and that something far more complex is going on. As the veteran researcher on obesity issues George Bray once said 'studying obesity isn't rocket science: it's far more complex.

The classical model for understanding why obesity develops is called the energy balance model[2]. That is a rather unfortunate name because it could be easily misinterpreted as being just a restatement of the law of energy balance. Indeed that accusation has been repeated several times in scientific papers[3-4] and popular books[5-6]. However, such misunderstandings do not do service to what is in fact a sophisticated physiological model of what is happening to regulate energy balance (hence its name)[7-8], and what goes wrong when we become obese. The fundamental idea of the EBM is that food intake is a response to the physiological needs of the body for energy and specific nutrients[9-10]. It isn't yet clear exactly how these needs are communicated to the brain but it seems that there are probably multiple pathways from diverse tissues, converging in the hypothalamus[11]. There is strong evidence that such needs drive food intake. For example, if you take a mouse and you transfer it from a standard room at 21°C into a cold room at 4°C, its energy needs go up enormously and within a couple of hours it starts to eat more food. The diverse body tissues talk to the

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brain about their requirements and the brain directs us to eat more or less food in response.

When food enters the body it sets off a cascade of responses in the alimentary tract. These include changes in levels of the nutrients themselves, various gastrointestinal hormones, direct nervous signals[12] and changes in the level of insulin. These signals are picked up in the brainstem and hypothalamus[13], so the gut is also talking to the brain about what is coming in to balance the needs for energy, and as those needs at the organs are fulfilled their cross talk to the brain is reduced. This system of balancing intake to needs works well, but it is dependent on there being sufficient food available in the environment for the needs to be satisfied. Probably for animals in the wild that isn't always the case so occasionally the calls from the tissue that the brain integrates as a signal to get more food, cannot be satisfied, and the animal finds itself with a shortfall of energy. For this eventuality the body carries several different stores of energy which include glycogen and body fat. These can be drawn on when the supply of energy doesn't meet the bodies needs. These stores also need to be regulated. In the case of fat stores the hormone leptin, and probably other adipokines, communicate to the brain the levels of the stored fat. Hence, the brain not only listens to the cross talk from the lean tissue about its needs, but also from the adipose tissue about the level of storage[14-16]. It then integrates these messages to direct the intake. If the adipose tissue fuel store is low then the consequent low leptin levels add to the impetus of the search to obtain energy from the environment[17-18].

If the energy available continues to remain inadequate then there is a risk the stores will run out. In that situation the brain not only needs to direct the search for food but also needs to communicate back to the tissues to regulate their use of energy - turning it down so that the fat lasts longer. That may involve just changes consequent of body composition changes[19] or be accompanied by tissue level alterations as well[20]. The brain therefore sits at the hub of a complex feedback network, regulating energy intake, but also regulating energy utilization so that an energy balance can be effected. By this model when you are under calorie restriction your energy needs go down[19-20]. There is considerable debate as to whether the converse occurs - that is when you over consume do you compensate by increasing your expenditure[1,21]. As you may now appreciate this Energy Balance Model is so much more than just a restatement of the laws of thermodynamics[22].

What goes wrong with this model and causes obesity? The answer is we don't exactly know. But it is obvious that the obesity problem has only happened over the last 60 years or so. Over this time period it isn't feasible there has been a big change in our genetics[23]. Hence, the trigger has to be something environmental. It is largely considered that the change in the environment is something about modern food that encourages us to overeat calories in relation to our needs[24]. It is like the brain instructs us to go into the ice cream shop to get some energy to meet our demands, but when it tells us that it's time to leave we just stay there and keep on eating. It seems that there are multiple causes of this effect - but among them are the reward properties of modern foods[25-27]. Modern foods seem to overwhelm our capacity to stop eating when our needs have been met. The problem then is in the brain. By the EBM model obesity is a brain malfunction. The brain is listening to the peripheral tissues about their needs but then it seems unable to listen to the other messages that those needs have been met.

The EBM model of obesity is the standard model that most obesity scientists believe and use in their work. It has been the basis for the development of drugs that have been successful but discontinued due to side effects, such as drugs that engage with cannabinoid signaling in the brain, and more recent drugs that hold considerable promise

for the future, including Glucagon like protein1 receptor antagonists that mimic the effect of a key gut hormone in the brain to trick the brain into eating less food[28]. In other words the drug mimics the gut-brain cross talk to solve the problem.

However, about 15 years ago a new idea was proposed. It is called the carbohydrate insulin model or CIM[2,4,6,29-32] and it proposes a fundamentally different dynamic for how food intake is regulated and why things go wrong in obesity. The basis of the CIM is that the locus of control is not the brain but the fat tissue[33]. It posits that the fat tissue calls the shots when it comes to regulating how much we eat. In effect we do not deposit fat because we eat too much energy, but rather we eat too much because our fat soaks up too much of the energy we consume and this drives us to eat more. In normal circumstances the adipose tissue is rather benign and doesn't have this sort of impact. It is suggested however that when we eat a certain type of carbohydrate, called high glycaemic index (GI) carbohydrates, this kicks off a disastrous chain of events. The high GI carbs flood the blood with glucose. That stimulates production of insulin and the spike of insulin packs the ingested energy away into the liver where lipogenesis is stimulated, leading to fat deposition in the adipose tissue. So, unlike the EBM, the storage of fat doesn't bear any strong relation to how much you eat, but is much more related to the type of food you eat - with high GI carbs being the main culprit[4,6,32,34]. The CIM suggests that what happens after this ingested fuel is packed away into the fat is the body senses that fuel levels have been depleted and that creates two responses - first energy expenditure is switched down, and second food intake is switched up. The mechanisms for these changes are not clear, i.e. whether the fat tissue communicates directly to tissues with high metabolism to suppress their use of energy, or if this action occurs via the brain. However, the sentiment of the model is that the locus of control over what happens is at the adipose tissue and not as the EBM suggests - the brain. So the tissue cross talk in this model is completely different. In the CIM the fat tissue is doing the talking.

The CIM suggests that the obesity epidemic has been caused by overconsumption of high glycaemic index carbohydrates like sugar[4,6,30,32,34]. The proposed solution to the epidemic then is to cut out these carbs from the diet, prevent the insulin spike happening and escape the vicious cycle of carb intake being soaked up by your fat, making you hungry and suppressing your metabolism, leading to further carb intake and more fat deposition. This idea struck a chord with people adopting low carbohydrate diets, such as those advocated originally by Dr Atkins in the 1970s and more recently by many others. By the CIM going onto a low carbohydrate diet is suggested to reduce hunger and boost your metabolism, and people on such diets often claim to lose weight effortlessly. Proponents of the CIM suggest this is because when you go onto a low carb diet you can effectively eat what you want because your energy expenditure is no longer suppressed by eating all those high GI carbohydrates. There are probably hundreds of people online advocating such diets based on their own personal weight loss success. Some of these advocates seriously think that they are eating 5 000 kcals/day and their metabolism has been boosted so that they are burning it all off. The carbohydrate-insulin model has therefore achieved a high level of support among non-scientists, in favor of the EBM which is the preferred model among most scientists. This conflict has been helped along in no small part by a prominent advocate of the CIM, who is a journalist, deriding mainstream nutrition scientists as not worthy of being called scientists, and accusing them of derailing the science of obesity by promoting a flawed model (i.e. the EBM)[6,35]. These insults are mostly based on the complete misconception that the energy balance model is just a tautology of the laws of physics.

On the face of it testing the predictions of the CIM in contrast to the EBM would seem easy. The CIM makes very clear predictions. As the % of high

GI carbohydrates in the diet are increased then we expect there will be a decrease in metabolic rate and an increase in food intake, and together these will promote a state of weight gain and ultimately obesity. Several attempts to test these predictions have been performed. However, doing the work in humans poses some problems. To control the diet carefully it is necessary to keep people on a metabolic ward where their intake can be closely controlled. This can only be done for relatively short periods, normally a couple of weeks. Such studies have tended to show no response in terms of energy expenditure and body weight when comparing between low carbohydrate and high carbohydrate feeding, or if anything reducing fat appears better than reducing carbohydrates[36-37]. But a major criticism of such studies is that perhaps they are just not long enough to have the desired impacts[3,30]. Allowing people to live more freely solves the duration issue, but brings another problem in that people who are not constrained may not stick to the diet[38-39]. So it is harder to infer what they actually ate[40], and what they ate is the key experimental variable. Although such studies have suggested there is a small increase in energy expenditure when dietary carbohydrate is reduced the effect is much smaller than anticipated and its magnitude disputed[3,41-42].

Studies in animals overcome these issues because it is possible to keep animals captive for much longer periods, and to always control very precisely what they eat. That control, however, may only come at the expense of translational relevance to humans. With that caveat in mind, however, my own group has performed an extensive diet study exposing mice to 24 different diets that varied widely in their carbohydrate, fat and protein contents[43-44]. The mice ate the diets for 12 weeks, which is equivalent to about 10 years in humans. The carbohydrates in the diets consisted of cornstarch and maltodextrin that are known to be high GI carbohydrates in mice. The responses in terms of their food intake and their body weights are shown in Fig. 1. It is clear from these plots that greater levels of carbohydrate were protective against weight gain mediated via lower food intake. Both these findings strongly refute the CIM, but advocates of that model are quick to point out the translational relevance might be an issue.

At the moment then we stand at an impasse. Studies that strictly control the diet in humans are potentially too short, studies that allow humans freedom can be longer but have poor dietary control, and strict studies of mice that overcome these two issues may have poor translational relevance. We still don't know then if the main way body fatness is regulated is because of the brain telling the fat what to do, or the fat telling the brain what to do. Understanding the nature of this inter-organ

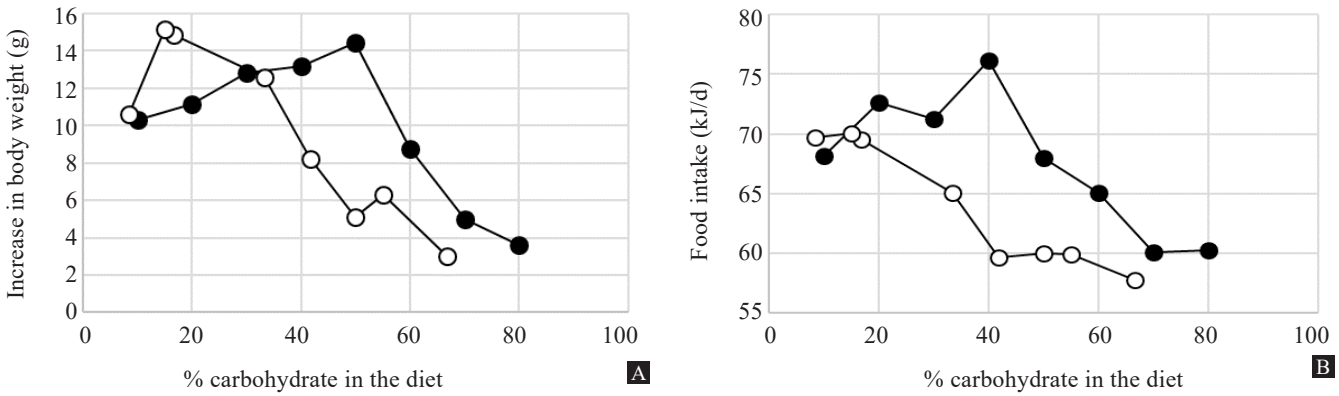

Fig. 1 Effects of carbohydrate content of the diet on body weight and food intake.

A. Increase in body weight over 12 weeks of feeding in relation to % carbohydrate content of the diet by energy at two levels of protein (25% in black and 10% in white); B. changes in food intake for the same mice in A. N per group is 20. Age of diet onset is 12 weeks. (data from[43-44]).

cross talk will require new approaches to break the impasse. In particular, we really need studies where individuals can have their diets strictly controlled, but over much more protracted periods of months, and maybe even years. How to achieve that will be difficult, but the insights emerging from such work would have important messages for our understanding of body fat regulation, and the pandemic of obesity.

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