Obesity as an Endocrine Disease: Theory and Clinical Application
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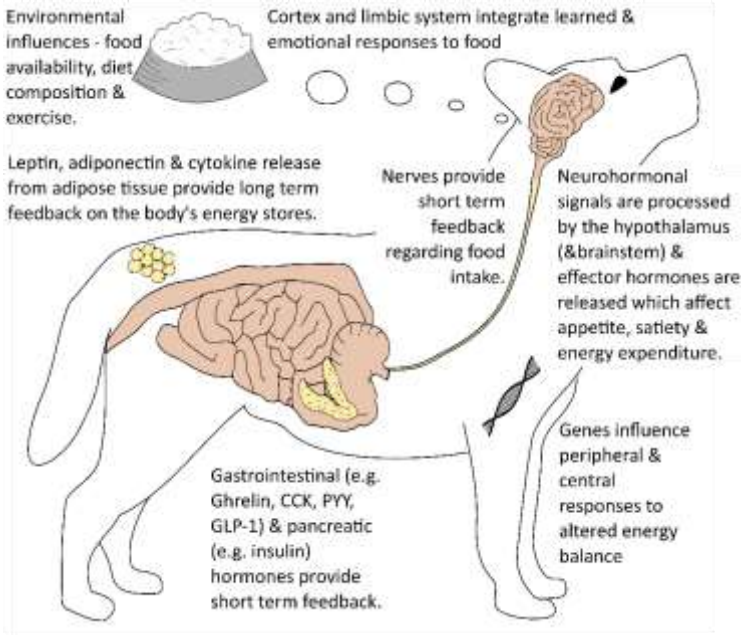
WHAT CAUSES OBESITY?

At its most simplistic, this is easy to answer – an individual piles on the pounds because there is a mismatch between energy intake and expenditure. That balance is most commonly affected by alterations in food intake and energy expended during exercise, but may also be influenced by the efficiency of substrate utilisation, factors that alter metabolic rate, and/or nutrient partitioning (storage of excess calories).

The veterinary literature has mainly focussed on how owners manage their dogs and has identified many predictable food and exercise related risk factors. But breed, age and gender also consistently identified as risk factors for obesity and remain there even when management factors are evened out in mathematical modelling, meaning their effect is physiological and independent of owners. So, while the physics of the energy balance equation between intake and expenditure is true, and owners should be able to control their dogs' food an exercise to keep them lean, it is disingenuous to dismiss the role of physiology in obesity development.

NEUROENDOCRINE CONTROL OF EATING BEHAVIOUR

The diagram below summarises the homeostatic mechanisms that occur to regulate eating behaviour and energy expenditure. It shows how messages from the gut and circulation about short term energy flux, and longer term messages from adipose tissue about energy stores, are sent via endocrine or neurological signalling pathways to the hypothalamus. There they are integrated to produce the sensations (hunger, satiation) and behavioural outcomes (food seeking, food choice, eating) that we are consciously aware of.



Long term signals – fat as an endocrine organ

Adipose tissue was long regarded as little more than an inert energy storage depot. However, it is better regarded as an endocrine organ. Adipose tissue secretes hormones (including leptin and adiponectin) and cytokines which travel in blood to exert distant effects. The amounts and types of these 'adipokines' released alter dependent on fat mass, so they act as distant signals of the body's energy reserves.

Key in the control of obesity is leptin, a hormone which is released in greater amounts from adipocytes which are lipid-rich. Thus its concentration increases in proportion to fat mass. Its key site of action is in the leptin-melanocortin signalling pathway in the hypothalamus, where it acts to reduce food intake so that when the body's energy reserves are replete, food seeking becomes less of a priority. When it was initially discovered, it was hoped that exogenous leptin might be a treatment for obesity but subsequently it became clear that the primary physiological role of leptin was as a marker for starvation rather than as a satiety signal; low leptin concentrations are potent stimulators of hunger and eating but the response to high levels is blunted (this is classically viewed as leptin resistance but may be part of normal physiology).

Leptin is released by adipose cells and travels in the circulation to act on leptin receptors expressed by specific neuronal populations in the arcuate nucleus of the hypothalamus which express the polypeptide pro-opiomelanocortin (POMC). POMC is processed by a series of enzymatic cleavages to produce a number of neuroactive ligands, the most relevant of which for energy homeostasis are α-MSH and β-MSH. The POMC neurons project to the paraventricular nucleus of the hypothalamus where release of α-MSH and β-MSH stimulate melanocortin 4 receptors (MC4R) which in turn project to other key brain nuclei and ultimately act to reduce food intake.

Downstream mediators likely to be involved in transducing the effects of MC4R activation on food intake regulation are brain-derived neurotrophic factor (BDNF), corticotropin-releasing hormone (CRH) and thyrotropin-releasing hormone (TRH). Recently, a mutation in POMC was identified in Labrador and flatcoat retrievers which is associated with eating behaviour and adiposity. The mutation disrupts production of β-MSH and so leptin melanocortin signalling, and in part responsible for the breed's notorious high food motivation and obesity predisposition.

Adiponectin is another much studied adipokine but its role is less well defined. Higher levels are produced when fat mass is low, and murine studies have suggested it may have a role as an insulin sensitizer. Evidence from humans is less clear, and canine studies conflict in their reports of adiponectin's association with adiposity.

Finally, inflammatory cells in adipose tissue have the potential to release both pro and anti-inflammatory cytokines. Their role will be discussed below.

Short term signals of satiety and energy balance

Whilst leptin is the major regulator of background hunger, gut and pancreatic hormones modulate the body's response to short term fluxes in energy, controlling meal-to-meal eating behaviour. The key 'hunger hormone' is ghrehlin which increases to a maximum just before a meal then drops after feeding. In contrast, a number of other hormones (glucagon-like peptide 1, peptide YY, oxyntomodulin, CCK) are responsible for detecting nutrients in the gut lumen or after absorption in circulation and promote satiety. Each are produced in response to different stimuli and frequently act not just to modulate eating behaviour but also to orchestrate the metabolic response to food.

Once again, the leptin melanocortin axis is centrally important in modulating this response. The key orexigenic neuronal population those expressing agouti related peptide, AgRP, in the arcuate nucleus of the hypothalamus. Like the POMC neurons, they receive hormonal and metabolic cues about nutritional status; AgRP concentrations are high during fasting and drop rapidly after eating. AgRP acts as an inverse agonist at MC4R, effectively antagonising the effect of MSH and stimulating food intake.

PHYSIOLOGICAL SET POINT IS INFLUENCED BY THE EXTERNAL ENVIRONMENT

Therefore, energy homeostasis is governed by leptin, gut peptides, other hormones including insulin, glucagon and thyroxine and metabolite levels. These act in concert to signal to the hypothalamus which integrates them and translates them into the behavioural outcomes which we observe as food seeking and eating. The central control of energy expenditure has been less well characterised, but it is likely that it is influenced by the leptin melanocortin axis and other pathways including sympathetic activation of brown fat depots, although the effect is subtle and the major homeostatic regulation of body weight is via the control of food intake.

There is a wealth of evidence that mammals regulate fat mass so that increases or reductions in adipose tissue mass activate responses that favor return to their original weight. Thus weight loss following caloric restriction is associated with reduced metabolic rate and increased appetite, and weight gain the opposite.

That might lead us to ask why (physiologically detrimental) obesity should develop. In reality, the core homeostatic drive exists alongside other relevant neurological inputs that superimpose themselves and drive the increased food intake that leads to weight gain. Cues related to food availability, taste and smell interact with hedonic pathways, integrating with inputs from past learning and memory and decision making centres. Evidence suggests that obtaining the pleasurable effects of food is a powerful motivating force that can override homeostatic satiety signals.

Thus ready availability and experience of highly palatable food is a powerful driver to increasing food intake beyond what is needed for maintenance of healthy body weight. This, alongside an increasingly sedentary lifestyle, is likely the key driver for the obesity epidemic seen in humans over the past 30 years. In dogs, it is likely that the same is true; reduced time spend outside (reducing the need for energy expenditure to maintain body heat) may also contribute.

NEW PLAYERS IN THE OBESITY GAME

In recent years there has been a rapidly evolving and increasingly convincing literature suggesting role for the microbiome in the development of obesity. Obesity is associated with different profiles of gut microbiota, but the jury is still out on the strength and mechanism of any causal association.

Additionally, new players in the regulation of energy homeostasis have emerged and their importance debated. For instance, the hormone resistin was initially heralded as an adipokine responsible for driving obesity-associated insulin resistance but subsequent data has been contradictory and suggests its role in modifying energy homeostasis is more nuanced and minor. Recent advances in our understanding of the biology of GDF15, a protein released in response to cellular stress, has demonstrated a role in regulating food intake, energy expenditure and body weight. It seems likely GDF15 is in fact responsible for governing aversive responses to food in disease rather than a core homeostatic mechanism *per se*.

PATHOPHYSIOLOGY OF OBESITY

Obesity is robustly associated with increased risk of many diseases in humans and companion animals. Attempting to identify a single inciting event at a molecular level is arguably unhelpful, but there are now multiple lines of evidence supporting what is known as the adipose expandability theory. In essence, it appears individuals have a limit to their ability to store fat healthily. Once that limit is met, lipid overspill and ectopic lipid accumulation in other tissues leads to insulin resistance and inflammation in multiple tissues.

Insulin Resistance Much of the research focus in the field has focussed on the development of insulin resistance and dyslipidaemia. That's largely because the constellation of hypertension, hyperglycaemia, increased visceral fat, and dyslipidaemia (commonly referred to as Metabolic Syndrome) which are commonly seen in obese people are major risk factors for heart disease, stroke and type II diabetes. In companion animals, obesity associated insulin resistance is a major clinical problem in horses (laminitis, equine metabolic syndrome) and cats (diabetes, hepatic lipidosis) and is also recognised in dogs (in which obesity related metabolic dysfunction is recognised in a subset of overweight dogs).

Multiple molecular mechanisms contribute to disruption of the normal response to insulin in the primary insulin responsive tissues (liver, fat and muscle). Ectopic lipid accumulation contributes both directly to disruption of intracellular signalling and normal glucose metabolism and indirectly by precipitating mitochondrial dysfunction and increasing production of reactive oxygen species (ROS). Together with inflammatory cytokines, these converge on the complex intracellular signalling pathways downstream of the insulin receptor to disrupt insulin signalling. Importantly, there is evidence of selectivity in which post-receptor pathways are affected in insulin resistance which has important ramifications in the association between insulin resistance and fatty liver or cancer.

The homeostatic drive to maintain normoglycaemia means the initial response to insulin resistance is to increase circulating insulin concentration. To begin with this allows maintenance of normoglycaemia. However, hyperinsulinaemia can further contribute to insulin resistance. Pancreatic beta cells, which are vulnerable to lipotoxicity, may eventually fail leading to intermittent (post meal) or persistent hyperglycaemia (diabetes).

Dyslipidaemia of obesity is characterised by hypertriglyceridemia and increased VLDL concentrations in humans and cats; dogs appear to develop obesity associated hypertriglyceridemia and increased cholesterol in all fractions. It develops in the insulin resistant state due to a combination of enhanced hepatic flux of fatty acids from dietary sources, intravascular lipolysis, and release from adipose tissue that have become resistant to the antilipolytic effects of insulin. In companion animals, dyslipidaemia is recognised in obesity but is not associated with the atherosclerosis common in humans.

In the liver, insulin normally leads to inhibition of gluconeogenesis and activation of lipogenesis. In obesity, insulin no longer suppresses hepatic gluconeogenesis, while continuing to activate lipogenesis, a state referred to as 'selective insulin resistance'. Consequently, hepatic lipid accumulates and excess lipid is exported as VLDL resulting in increased plasma triglycerides. In humans, obesity-associated NAFLD and related non-alcoholic steatohepatitis (NASH) are major clinical problems. Hepatic lipid accumulation in obese dogs and cats has also been documented and likely plays a role in the pathogenesis of hepatic lipidosis in cats and increased liver enzymes in overweight dogs.

Insulin is an anabolic hormone and a number of trophic syndromes are associated with chronic hyperinsulinaemia in humans, notably polycystic ovary syndrome and acanthosis nigricans. These are likely to be a consequence of off-target insulin stimulation of the IGF1 receptor (which is structurally very similar to the insulin receptor) and/or selective insulin resistance that affects only part of the signalling cascade downstream of the insulin receptor. Similarly, promotion of cell growth and proliferation due to hyperinsulinaemia is implicated in the association between obesity and cancer, which is well established in humans and for which there is emerging evidence in dogs and cats.

Inflammation Obesity is associated with chronic low grade inflammation, primarily due to release of pro-inflammatory cytokines from adipose tissue macrophages. Lipotoxicity, local hypoxia in expanding adipose tissue, mechanical stress on adipocytes, and circulating gut-derived LPS (intestinal permeability is increased in obesity) are all implicated as inciting events in adipose inflammation. The predominant cells responsible for releasing proinflammatory cytokines are adipose tissue macrophages which switch from M2-polarized to M1-polarized (pro-inflammatory) as obesity develops, leading to release of cytokines such as TNF-α, IL-1β and IL-6, and C-reactive protein.

There is now robust evidence that obesity-associated inflammation contributes to the development of IR by mechanisms that converge to activate serine kinases that directly block insulin action. Inflammation is also implicated in the obesity-cancer association and in exacerbating other obesity associated diseases such as (human) asthma or osteoarthritis.

CONCLUSION

Obesity develops as a consequence of the body's normal homeostatic mechanisms to regulate fat mass being overridden by environmental factors. Key mechanisms by which obesity leads to disease are insulin resistance and inflammation.

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