Obesity Is a Disease

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Clinicians understand the risks of being obese and encourage patients to lose weight to prevent the complications of obesity. Thus far, it has been very difficult to treat obesity as the aetiology has been misunderstood. Logically, if clinicians can convince themselves that obesity is a disease that requires treatment, then progress can be made. Most human diseases are characterised by a set of reproducible symptoms and signs which affect a particular group of people and follow a predictable clinical trajectory (Jones et al. 2012). Our understanding of the disease is enhanced when its aetiology and complications are well defined. Obesity can now be defined as a disease characterised by the pathognomonic symptoms of excessive hunger and/or reduced satiation after a meal and the pathognomonic sign of increased adiposity, resulting in a state of dysregulated energy homeostasis that substantially increases mortality (Fontaine et al. 2003). Subcortical brain regions, especially the hypothalamus, integrate a diverse array of hormonal and nerve signals from the viscera and brain to govern human feeding behaviours (Saper and Lowell 2014). Evidence has been mounting that will help clinicians understand that by approaching obesity as a disease of the subcortical brain regions, more effective and compassionate treatments can be provided to our patients.

For clinicians, the most striking clinical example is when a child who is of normal weight and living in an optimal environment as regards food intake develops a

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craniopharyngioma. These benign cystic epithelial tumours of the sellar or suprasellar region frequently affect the hypothalamus, thus offering an opportunity to gain clinical insights into the role the hypothalamus plays in obesity. Prevalence of hypothalamic dysfunction in children with craniopharyngiomas increases from approximately 35% at diagnosis to 65–80% after treatment (Muller 2016). In a review of 24 cases of paediatric craniopharyngiomas, body-mass index (BMI) increased by 6.8 kg/m^2 and 13 children deteriorated from being normal weight to become obese (BMI >95th percentile for age) at 5 years from diagnosis (Rosenfeld et al. 2014). Risk factors for obesity in children with craniopharyngiomas include preoperative hypothalamic dysfunction, intra-hypothalamic location of the tumour, hypothalamic radiation therapy, and hypothalamic injury at the time of surgery (Rosenfeld et al. 2014). The prevalence of postoperative severe obesity is approximately halved in children who undergo hypothalamus-sparing surgery compared with children who undergo extensive resections involving the hypothalamus (Elowe-Gruau et al. 2013). Weight gain in children with craniopharyngiomas occurs despite replacement of pituitary hormone deficiencies and is greater than for other causes of pituitary dysfunction (Geffner et al. 2004). Obesity in children with craniopharyngiomas occurs even when their caloric intake is similar to controls matched for BMI (Harz et al. 2003). Pathological eating behaviours in survivors of childhood-onset craniopharyngioma with varying degrees of obesity are similar or even less compared with BMI-matched controls (Hoffmann et al. 2015). Rather, craniopharyngioma-associated obesity is characterised by reduced basal metabolic rate, reduced physical activity, and impaired feedback signalling from leptin, ghrelin, and insulin (Holmer et al. 2010).

Another clinical dogma is that patients with obesity only need to eat less and exercise more. As a consequence of this conventional paradigm, we suggest to patients that more motivation and self-control will by itself suffice to achieve control of body weight. While inputs from forebrain areas dealing with reward, motivation, and decision-making probably influence hypothalamic neuronal circuits to play an ancillary role in the control of appetite and body weight, neuroendocrine regulation coordinated by the hypothalamus, and not a lack of self-discipline, is the principal determinant of energy homeostasis (Saper and Lowell 2014).

Indeed, if motivation was critical then conditions that impair cortical brain function resulting in a loss of motivation, such as Alzheimer's disease and traumatic brain injury, should be accompanied by profound changes in body weight. Contrary to this dogma, weight loss and not gain predicts progression of mild cognitive impairment to dementia and has been identified as a risk factor for the onset of dementia in observational studies (Sergi et al. 2013); however, absolute changes in body weight of more than 4% over 3 years are rare (Cova et al. 2016). Furthermore, mean BMI was not significantly different to baseline values at median 3-year follow-up of 107 adults with traumatic brain injury (Crenn et al. 2014).

Clinical therapeutics are enhanced if underlying disease mechanisms are understood or if even as clinicians, we know which organ we are treating. Brain lesioning experiments involving rodents demonstrated that ventromedial (VMH) and lateral (LH) hypothalamic injury resulted in dramatic hyperphagia or hypophagia,

respectively (Hetherington 1944; Hetherington and Ranson 1942; Teitelbaum and Epstein 1962; Baillie and Morrison 1963). These experiments were the foundation of understanding eating behaviours: inhibitory and excitatory signals from the VMH and LH were partly responsible for satiety and hunger, respectively (Stellar 1954). The VMH receives afferent input from the viscera, such as insulin from the pancreas, leptin from adipose cells, ghrelin from the stomach, and peptide YY from the small intestine. VMH injury disrupts communication between the viscera and central nervous system regarding energy stores and energy intake (Saper and Lowell 2014). Independent of hyperphagia, VMH injury has been shown to cause severe obesity by altering autonomic function to result in impaired fat metabolism, hyperinsulinaemia, and markedly increased gastric acid secretion and gastric emptying (King 2006).

Other subcortical brain centres such as the arcuate nucleus, paraventricular nucleus, and medial amygdala are increasingly recognised to interact with the VMH to modify food intake and body weight (King 2006). As the complex pathways involving several brain regions which underpin hypothalamic obesity continue to be unravelled, the concept of discrete feeding centres outlined above is being modified. Nevertheless, the importance of the VMH and LH in integrating afferent signals as part of a broader network governing hunger and satiety remains undisputed and helps us to understand that if our treatments do not make patients less hungry and/or more satisfied after smaller meals, then our chances of achieving durable weight loss will be limited.

The aetiology of obesity is heterogeneous and poorly understood, but recent advances in molecular biological techniques have facilitated an improved understanding of its pathophysiology and heritability. Obesity is rarely inherited in a Mendelian pattern: syndromic (e.g. Prader-Willi syndrome) and non-syndromic (e.g. leptin and leptin receptor mutations) monogenic obesity may result from mutations in single genes encoding proteins involved in hypothalamic pathways regulating energy homeostasis (Mutch and Clement 2006). Monogenic obesity is characterised by a severe phenotype with the onset of obesity in early life irrespective of environmental stimuli. Conversely, there is a global pandemic of polygenic obesity in which single nucleotide polymorphisms and epigenetic alterations in DNA methylation of multiple genes predisposing to adipose tissue expansion are exacerbated by an environment that favours energy consumption over energy expenditure (Pigeyre et al. 2016). Family history of obesity is a strong risk factor for childhood obesity (Birbilis et al. 2013), and obesity prevalence varies according to ethnicity (Pigeyre et al. 2016), suggesting that obesity is a heritable disorder. Both genetic and environmental factors account for the familial aggregation of obesity phenotypes (Chaput et al. 2014), although twin studies have illustrated that genetic factors are the dominant force and account for approximately 77% of the variance in BMI and waist circumference (Wardle et al. 2008).

Obesity complications are well defined, and their rising prevalence presents one of the foremost challenges to healthcare delivery in the twenty-first century. Importantly, many complications including hypertension (Schiavon et al. 2017), type 2 diabetes mellitus (Schauer et al. 2017), obstructive sleep apnoea (Ashrafian

et al. 2015), idiopathic intracranial hypertension (Manfield et al. 2017), polycystic ovarian syndrome (Nicholson et al. 2010), and non-alcoholic fatty liver disease (Bower et al. 2015) can be reversed with intentional weight loss. Indeed, large observational studies have demonstrated that sustained weight loss achieved with bariatric surgery reduces mortality by 29–40% (Sjostrom et al. 2007; Adams et al. 2007).

In conclusion, obesity is a subcortical brain disease characterised by the pathognomonic symptoms of excessive hunger and/or reduced satiation after a meal. Distinct subtypes of obesity are recognised, although the rising incidence of polygenic obesity resulting from incompletely elucidated gene-environment interactions is of greatest public health concern. Obesity complications are well documented; their reversal with sustained intentional weight loss is a reason for optimism and motivation to seek treatments targeting pathophysiological mechanisms of obesity. Although lifestyle modification to achieve net energy deficit represents an important facet of obesity management, it is imperative to remember that hypothalamic dysfunction underpins this dysregulated state of energy metabolism and that solely appealing to patients' cerebral cortices through motivational strategies will ultimately prove futile for many. Most patients will regain all the weight that they have lost if the treatment strategy does not make them less hungry and/or more satisfied with smaller meals (Dombrowski et al. 2014). Instead, we must expand our understanding of the pathophysiology of obesity and target our treatments to correct the subcortical brain disturbances which perpetuate aberrant feeding behaviours. Until our clinical tools improve, we can serve our patients better by recognising obesity as a disease and treating it with the same strategies and compassion we apply to all other chronic and disabling diseases.

References

Adams TD, Gress RE, Smith SC, Halverson RC, Simper SC, Rosamond WD, et al. Long-term mortality after gastric bypass surgery. N Engl J Med. 2007;357(8):753–61.

Ashrafian H, Toma T, Rowland SP, Harling L, Tan A, Efthimiou E, et al. Bariatric surgery or non-surgical weight loss for obstructive sleep apnoea? A systematic review and comparison of meta-analyses. Obes Surg. 2015;25(7):1239–50.

Baillie P, Morrison SD. The nature of the suppression of food intake by lateral hypothalamic lesions in rats. J Physiol. 1963;165(2):227–45.

Birbilis M, Moschonis G, Mougios V, Manios Y. Obesity in adolescence is associated with perinatal risk factors, parental BMI and sociodemographic characteristics. Eur J Clin Nutr. 2013;67(1):115–21.

Bower G, Toma T, Harling L, Jiao LR, Efthimiou E, Darzi A, et al. Bariatric surgery and non-alcoholic fatty liver disease: a systematic review of liver biochemistry and histology. Obes Surg. 2015;25(12):2280–9.

Chaput JP, Perusse L, Despres JP, Tremblay A, Bouchard C. Findings from the Quebec family study on the etiology of obesity: genetics and environmental highlights. Curr Obes Rep. 2014;3:54–66.

Cova I, Clerici F, Rossi A, Cucumo V, Ghiretti R, Maggiore L, et al. Weight loss predicts progression of mild cognitive impairment to Alzheimer's disease. PLoS ONE. 2016;11(3):e0151710.

Crenn P, Hamchaoui S, Bourget-Massari A, Hanachi M, Melchior JC, Azouvi P. Changes in weight after traumatic brain injury in adult patients: a longitudinal study. Clin Nutr (Edinburgh, Scotland). 2014;33(2):348–53.

Dombrowski SU, Knittle K, Avenell A, Araújo-Soares V, Sniehotta FF. Long term maintenance of weight loss with non-surgical interventions in obese adults: systematic review and meta-analyses of randomised controlled trials. Br Med J. 2014;348

Elowe-Gruau E, Beltrand J, Brauner R, Pinto G, Samara-Boustani D, Thalassinos C, et al. Childhood craniopharyngioma: hypothalamus-sparing surgery decreases the risk of obesity. J Clin Endocrinol Metab. 2013;98(6):2376–82.

Fontaine KR, Redden DT, Wang C, Westfall AO, Allison DB. Years of life lost due to obesity. JAMA. 2003;289(2):187–93.

Geffner M, Lundberg M, Koltowska-Haggstrom M, Abs R, Verhelst J, Erfurth EM, et al. Changes in height, weight, and body mass index in children with craniopharyngioma after three years of growth hormone therapy: analysis of KIGS (Pfizer International Growth Database). J Clin Endocrinol Metab. 2004;89(11):5435–40.

Harz KJ, Muller HL, Waldeck E, Pudel V, Roth C. Obesity in patients with craniopharyngioma: assessment of food intake and movement counts indicating physical activity. J Clin Endocrinol Metab. 2003;88(11):5227–31.

Hetherington AW, Ranson SW. The relation of various hypothalamic lesions to adiposity in the rat. J Comp Neurol. 1942;76(3):475–99.

Hetherington AW. Non-production of hypothalamic obesity in the rat by lesions rostral or dorsal to the ventro-medial hypothalamic nuclei. J Comp Neurol. 1944;80(1):33–45.

Hoffmann A, Postma FP, Sterkenburg AS, Gebhardt U, Muller HL. Eating behavior, weight problems and eating disorders in 101 long-term survivors of childhood-onset craniopharyngioma. J Pediatr Endocrinol Metab. 2015;28(1-2):35–43.

Holmer H, Pozarek G, Wirfalt E, Popovic V, Ekman B, Bjork J, et al. Reduced energy expenditure and impaired feeding-related signals but not high energy intake reinforces hypothalamic obesity in adults with childhood onset craniopharyngioma. J Clin Endocrinol Metab. 2010;95(12):5395–402.

Jones DS, Podolsky SH, Greene JA. The burden of disease and the changing task of medicine. N Engl J Med. 2012;366(25):2333–8.

King BM. The rise, fall, and resurrection of the ventromedial hypothalamus in the regulation of feeding behavior and body weight. Physiol Behav. 2006;87(2):221–44.

Manfield JH, Yu KK, Efthimiou E, Darzi A, Athanasiou T, Ashrafian H. Bariatric surgery or non-surgical weight loss for idiopathic intracranial hypertension? A systematic review and comparison of meta-analyses. Obes Surg. 2017;27(2):513–21.

Muller HL. Craniopharyngioma and hypothalamic injury: latest insights into consequent eating disorders and obesity. Curr Opin Endocrinol Diabetes Obes. 2016;23(1):81–9.

Mutch DM, Clement K. Unraveling the genetics of human obesity. PLoS Genet. 2006;2(12):e188.

Nicholson F, Rolland C, Broom J, Love J. Effectiveness of long-term (twelve months) nonsurgical weight loss interventions for obese women with polycystic ovary syndrome: a systematic review. Int J Womens Health. 2010;2:393–9.

Pigeyre M, Yazdi FT, Kaur Y, Meyre D. Recent progress in genetics, epigenetics and metagenomics unveils the pathophysiology of human obesity. Clin Sci (London, England). 2016;130(12):943–86.

Rosenfeld A, Arrington D, Miller J, Olson M, Gieseking A, Etzl M, et al. A review of childhood and adolescent craniopharyngiomas with particular attention to hypothalamic obesity. Pediatr Neurol. 2014;50(1):4–10.

Saper CB, Lowell BB. The hypothalamus. Curr Biol. 2014;24(23):R1111-6.

Schauer PR, Bhatt DL, Kirwan JP, Wolski K, Aminian A, Brethauer SA, et al. Bariatric surgery versus intensive medical therapy for diabetes—5-year outcomes. N Engl J Med. 2017;376(7):641–51.

Schiavon CA, Bersch-Ferreira AC, Santucci EV, Oliveira JD, Torreglosa CR, Bueno PT, et al. Effects of bariatric surgery in obese patients with hypertension: The GATEWAY randomized trial (gastric bypass to treat obese patients with steady hypertension). Circulation. 2017;

Sergi G, De Rui M, Coin A, Inelmen EM, Manzato E. Weight loss and Alzheimer's disease: temporal and aetiologic connections. Proc Nutr Soc. 2013;72(1):160–5.

Sjostrom L, Narbro K, Sjostrom CD, Karason K, Larsson B, Wedel H, et al. Effects of bariatric surgery on mortality in Swedish obese subjects. N Engl J Med. 2007;357(8):741–52.

Stellar E. The physiology of motivation. Psychol Rev. 1954;61(1):5–22.

Teitelbaum P, Epstein AN. The lateral hypothalamic syndrome: recovery of feeding and drinking after lateral hypothalamic lesions. Psychol Rev. 1962;69:74–90.

Wardle J, Carnell S, Haworth CM, Plomin R. Evidence for a strong genetic influence on childhood adiposity despite the force of the obesogenic environment. Am J Clin Nutr. 2008;87(2):398–404.