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Vitamin D deficiency is the cause of common obesity

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SUMMARY

Common obesity is associated with the metabolic syndrome and can be distinguished from secondary obesity and from rare forms of monogenic and polygenic obesity. The prevalence of common obesity has become a public health concern in many countries as phenomenological approaches to the understanding of obesity have failed to achieve any long term effect on prevention or treatment. There is evidence for a central control mechanism which maintains body-weight to a set-point by the regulation of energy intake and energy expenditure through homeostatic pathways. It is suggested in this paper that common obesity occurs when the set-point is raised and that accumulation of fat mass functions to increase body size. Larger body size confers a survival advantage in the cold ambient temperatures and food scarcity of the winter climate by reducing surface area to volume ratio and by providing an energy store in the form of fat mass. In addition, it is suggested that the phenotypic metabolic and physiological changes observed as the metabolic syndrome, including hypertension and insulin resistance, could result from a winter metabolism which increases thermogenic capacity. Common obesity and the metabolic syndrome may therefore result from an anomalous adaptive winter response. The stimulus for the winter response is proposed to be a fall in vitamin D. The synthesis of vitamin D is dependent upon the absorption of radiation in the ultraviolet-B range of sunlight. At ground level at mid-latitudes, UV-B radiation falls in the autumn and becomes negligible in winter. It has previously been proposed that vitamin D evolved in primitive organisms as a UV-B sensitive photoreceptor with the function of signaling changes in sunlight intensity. It is here proposed that a fall in vitamin D in the form of circulating calcidiol is the stimulus for the winter response, which consists of an accumulation of fat mass (obesity) and the induction of a winter metabolism (the metabolic syndrome). Vitamin D deficiency can account for the secular trends in the prevalence of obesity and for individual differences in its onset and severity. It may be possible to reverse the increasing prevalence of obesity by improving vitamin D status.

Introduction

Obesity is a clinical condition in which there is an above-normal mass of adipose tissue, usually defined by a Quetelet Index, or body mass index (BMI), of 30 kg/m^2 or higher, and which is associated with increased morbidity and reduced mortality [1]. The prevalence and severity of obesity has increased in the past 30 years and is presently a public health concern in many countries. Common obesity can be distinguished from rare forms of monogenic obesity, such as leptin deficiency, in which the obesity is often accompanied by characteristic behavioural, developmental and endocrine disorders; from syndromic obesity, such as Prader-Willi syndrome (PWS), in which chromosomal abnormalities result in obesity, developmental abnormalities and other distinct phenotypic features; and from endocrine disorders, such as Cushing's syndrome, in which obesity is secondary to the primary disorder. Common obesity is postulated to result from a complex genes–environment interaction [2]. It is thought that excessive adipose mass is directly related to an accumulation of surplus energy due to an imbalance between energy intake from the diet and energy output in the form of physical activity. The energy excess is thought to occur when a thrifty genotype is combined with the environment typical of the modern urban-industrial society, in which there is food abundance combined with a low demand for physical activity. The thrifty genotype hypothesis, first put forward by Neel in 1962, is that a highly efficient metabolism evolved under the pressure of a negative energy environment [3]. In the context of an environment with an energy surfeit – the so-called "obesogenic" environment – weight gain is facilitated and obesity is an inevitable consequence. A weakness of this hypothesis is that, whilst the obesogenic environment can explain the geographical distribution and the secular trends in the prevalence of obesity, it cannot account for the variance in BMI between individuals in the same environment; and whilst genetic variation can explain the differences between individuals in the same environment, it cannot explain the secular trends or the initiation of weight gain at a particular point in the life course of the individual. Evidence for the energy surfeit of the environment as a cause of obesity is weak [4–6] and, despite progress made in identifying quantitative trait loci associated with obesity, genetic disorders of energy bal-

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ance appear to be rare [7]. In addition, the failure of weight loss intervention, which attempts to reverse the environmental effects, to achieve enduring weight loss, suggests the existence of an unrecognised aetiological factor which interacts between the thrifty genotype and the obesogenic environment. The hypothesis presented herein is that vitamin D deficiency is the cause of obesity and that obesity can be reversed by improving vitamin D status. In outline, it is proposed that common obesity results from an anomalous adaptation to a cold climate which is induced by a fall in vitamin D. A pivotal assumption is that vitamin D originated as a photoreceptor system in primitive organisms, and although it subsequently evolved into a regulator of differentiation, it retained its original role as an ultraviolet (UV)-B radiation-sensitive sensor which serves to signal changes in sunlight intensity. A fall in UV radiation in the autumn is proposed to be the environmental cue for an acclimatory or adaptive response which enhances winter endurance. The winter response entails an increase in body size by the accumulation of fat mass (obesity), which reduces heat conductance to the environment; and the induction of a winter metabolism (the metabolic syndrome), which increases thermogenic capacity. It follows that the production of vitamin D inhibits this response and it may be possible to prevent and treat obesity and the metabolic syndrome by improving vitamin D status. Common obesity has become prevalent in recent decades because of a lack of vitamin D in the urban-industrial environment which is a constructed tropical microclimate created by means of artificial sources of visible radiation (light) and infra-red radiation (heat), but not UV radiation. Endogenous production of vitamin D is redundant in organisms that can obtain sufficient vitamin D from the diet. This dietary supply has enabled organisms to occupy habitats without daily sunlight. Conversely, dietary supply is not required in organisms that have unlimited exposure to sunlight. In the modern urban-industrial environment, both the dietary supply and sunlight exposure have become inadequate to maintain a healthy vitamin D status in the majority of the human population. In the following section the evidence for the main assumptions of the hypothesis is presented in a step-by-step manner. These assumptions challenge the phenomenological approach which dominates the study of obesity. The cause of the increase in the prevalence of obesity and the implications of the hypothesis are examined in the discussion section.

Common obesity is a winter response

Weight gain is a controlled physiological process

Body-weight is normally stable, even in obesity in which a period of weight gain is often followed by a period of weight stability [8]. It is conceivable that in the normal state, maintenance of a steady body-weight should persist throughout adulthood, controlled by a self-regulating loop since, in common with other physiological systems, homeostastic mechanisms exist for the regulation of weight by the regulation of energy balance [8,9]. Recent research has identified multiple signals and pathways involved in energy homeostasis, which support the adipostat model proposed by Kennedy, in which the amount of energy stored by the body in adipose tissue is monitored by centres in the brain sensitive to the concentrations of circulating signals, and maintained at a constant level by controlling energy intake and energy expenditure [10]. Circulating signals include those secreted by adipose tissue (leptin, adiponectin, resistin), the pancreas (insulin, pancreatic polypeptide), and the gut (peptide YY, ghrelin, glucagon-like peptide-1, oxyntomodulin, cholecystokinin, bombesin) [11]. Integration of these signals and regulation of energy intake and energy expenditure occur in areas of the hypothalamus and the brain stem [12]. Two neuronal circuits which project from the arcuate nucleus (ARC) to the paraventricular nucleus (PVN) in the hypothalamus play a major role in energy homeostasis [13]. The first of these circuits consists of a population of neurons which express pro-opiomelanocortin (POMC) peptides and cocaine- and amphetamine-regulated transcript (CART), and the second is comprised of neurons which express agouti-related protein (AgRP) and neuropeptide Y (NPY). The emerging picture is one of a dual regulatory system which can be compared to that of thermoregulation. In essence, POMC/CART neurons are anorexigenic and promote energy dissipation, while AgRP/NPY neurons are orexigenic and promote energy accrual. Activation of the AgRP/NPY neurons, for example, stimulate feeding *via* PVN NPY receptors, inhibit the melanocortin system *via* ARC Y_1 receptors and antagonise the melanocortin receptors, MC3-R and MC4-R [13]. Leptin is a hormone secreted by adipocytes and circulating leptin concentration is directly proportional to fat mass [14]. Leptin inhibits the NPY/AgRP neurons and activates the POMC/CART neurons, *via* the Ob-Rb receptor which is expressed in the hypothalamus. After a period of fasting there is a restorative response in which the decline in fat mass and subsequent fall in the circulating concentration of leptin results in an inhibition of the POMC pathway, allowing an increase in food intake and reduction in energy expenditure [15]. It is intuitive that after a period of excessive energy intake resulting in an increase in adiposity, there should be an opposite response in which raised leptin activates the POMC pathway, thereby reducing food intake and increasing the metabolic rate, to restore fat mass to normal. In common obesity, although there is an increase in leptin, the expected restorative response is not observed and its absence is assumed to be due to either a bias in the system towards energy accrual, or a defect in the energy homeostatic pathways [16]. Mutations in the genes for POMC, either of the melanocortin receptors MC3-R and MC4-R, and leptin are associated with the obese phenotype; however, these mutations are rare and cannot account for the prevalence of common obesity. The proposal that the homeostatic system is biased towards protection from starvation and that there is no upper threshold above which energy dissipation is induced is countered by the relative stability of body-weight and by the existence of the anorexigenic POMC/CART neuronal pathway, which opposes the AgRP/NPY pathway. An alternative explanation is that, in accordance with Kennedy's hypothesis, the homeostatic system works to a set-point, in a similar manner to the set-point for temperature, with mutually antagonistic neuronal inputs. In this model, common obesity occurs when the body-weight set-point has been raised, appetite is increased and activity levels are reduced, and fat is accumulated until the elevated set-point has been reached. Higher leptin concentrations caused by the increase in adipose mass, do not inhibit NPY/AgRP or activate POMC/CART until the elevated set-point is attained. In support of this model, common obesity has characteristics in common with starvation and fasting, such as raised intramuscular triglyceride (IMTG) content [17]. Dietary interventions for weight loss are accompanied by physical and emotional discomfort and enduring weight loss is difficult to achieve. Several studies have shown that a reduction in energy expenditure, due to both lowered physical activity and resting metabolic rate, follows a period of restricted energy intake [18]. In one study, for example, the energy requirements of obese patients with a mean weight of 152 ± 8.4 kg fell from 3651 to 2171 kcal/d after weight was reduced to 100.2 ± 5.7 kg. This was lower than the 2280 kcal/d required by control patients, who had never been obese and had a mean weight of 62.6 ± 2.3 kg [19]. These observations become clearly understood when it is assumed that obesity results from a physiological state of energy accrual. In summary, it can be assumed that weight gain is a regulated process, and that