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The pathogenesis of obesity

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ABSTRACT

Body fat mass increases when energy intake exceeds energy expenditure. In the long term, a positive energy balance will result in obesity. The worldwide prevalence of obesity has increased dramatically, posing a serious threat to human health. Therefore, insight in the pathogenesis of obesity is important to identify novel prevention and treatment strategies. This review describes the physiology of energy expenditure and energy intake in the context of body weight gain in humans. We focus on the components of energy expenditure and the regulation of energy intake. Finally, we describe rare monogenetic causes leading to an impairment in central regulation of food intake and obesity.

1. Introduction

The first law of thermodynamics states that energy can neither be created nor destroyed [1]. Humans obtain all energy from ingested food and drink, store it as high-energy molecules, and expend it during basal metabolic functions, activity, and thermogenesis. In the steady state, the body's energy inputs balance the sum of energy outputs. However, when energy consumption exceeds energy expenditure, 60–80% of energy surplus is stored as fat [2]. The remainder is stored as glycogen, used for the biosynthesis of proteins, or is lost, e.g., during thermogenesis [2].

Overweight and obesity are characterized by excess amounts of body fat. They are usually defined as body mass index (BMI) ≥25 and ≥30 kg/m^2, respectively, although BMI does not differentiate between lean and fat mass and provides no information on body fat distribution. Central obesity is a debilitating medical condition, associated with a range of metabolic disorders, such as dyslipidemia, hypertension, and hyperglycemia, collectively known as the metabolic syndrome [3]. This constellation of comorbidities confers a fivefold risk of type 2 diabetes mellitus (T2DM) and a significantly increased risk of cardiovascular diseases compared to individuals without metabolic syndrome [4]. Currently, 1.3 billion people around the world are overweight or obese [5]. As such, obesity is the fifth greatest cause of non-communicable diseases [6].

In this review, we aim to shed light on the physiology of energy balance regulation and pathophysiology of human obesity. We focus on human mechanisms of energy intake and energy expenditure and provide an overview of monogenetic causes of obesity.

2. Energy Expenditure

Energy expenditure (EE) consists of three components: resting metabolic rate (RMR), activity-related energy expenditure (AEE), and (diet-induced) thermogenesis (DIT) [7]. The metabolism of an individual at rest is known as the RMR, i.e., the energy requirements for maintenance of vital body functions, such as temperature, circulation, respiration, and cell growth. In sedentary adults, RMR accounts for 60–75% of total daily EE [8]. A major determinant of RMR is body composition, specifically that of metabolically active tissues such as fat-free

Abbreviations: ACTH, adrenocorticotropin hormone; AEE, activity-related energy expenditure; AgRP, activity-related energy expenditure; ATP, adenosine triphosphate; BMI, body mass index; cholecystokinin, CCK; CNS, central nervous system; CRISPR, clustered regularly interspaced short palindromic repeats; Cas, CRISPR associated protein; D2/3(R), dopamine 2/3 (receptor); DIO, diet-induced obesity; DIT, diet-induced thermogenesis; RMR, resting metabolic rate; EAT, exercise activity thermogenesis; EE, energy expenditure; FFM, fat-free mass; fMRI, functional magnetic resonance imaging; FTO, fat mass and obesity associated; GLP-1, glucagon-like peptide 1; GWAS, genome wide association studies; LEP(R), leptin (receptor); LPS, lipopolysaccharides; MC3/4(R), melanocortin 3/4 (receptor); MRAP2, melanocortin-2 receptor accessory protein 2; NEAT, non-exercise activity thermogenesis; NPY, neuropeptide Y; PCSK1, proprotein convertase subtilisin/kexin type 1; PET, positron emission tomography; POMC, pro-opiomelanocortin; PYY, peptide YY; SCN, suprachiasmatic nucleus; SNS, sympathetic nervous system; SPECT, single photon emission tomography; T2DM, diabetes mellitus type 2; α-MSH, α-melanocyte-stimulating hormone.

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mass (FFM). Daily intra- and inter-individual variability in RMR ranges from 2 to 10% [9–13] and 7.5 to 17.9% [14–16], respectively. In general, women have lower RMR than men [17–21], and young adults have higher RMR than older adults [19,22,23], which may be attributed to differences in skeletal muscle mass [24,25]. Notably, however, there is much variation in metabolic rate: at any given body size, subjects can have low, normal, or high metabolic rates [26]. Sixty-two percent of the inter-individual variation is attributable to the amount of FFM [27]. Fat mass and age accounts for 6 and 2%, respectively [27]. The remainder (26.7%) is unexplained [27]. Nevertheless, when comparing individuals of similar FFM, differences up to 715 kcal/day are found [28]. Hereditability plays a role as well. Twin studies have shown that genetics account for approximately 40% of RMR [29]. Several studies identified low RMR as a risk factor for weight gain [30,31]. The risk of gaining 10 kg of body weight is approximately eight times greater in individuals belonging to the lowest tertile of RMR compared to those in the highest tertile [26].

AEE can be categorized into exercise activity thermogenesis (EAT) and non-exercise activity thermogenesis (NEAT) [2]. Generally, the contribution of EAT to total daily EE is negligible [32], and NEAT is predominant [8]. NEAT comprises EE during all physical activities other than sport-like exercises, such as occupational EE and leisure-time physical activity [32]. It varies widely across and within individuals on a daily basis and can differ up to 2000 kcal/day between two individuals of similar size [32]. The variability in NEAT is in part genetically determined [33].

Energy intake, ironically, also adds to EE, as energy is necessary for the foraging, digestion, absorption, and storage of food [2]. DIT is the increase in metabolic rate associated with the ingestion of food and increases in post-absorptive heat production [34]. Typically, DIT accounts for 5–15% of total EE [35]. The magnitude of the thermic effect of food depends on the energy content and composition of the food consumed. Measured thermic effects of nutrients are 5–15% for carbohydrates and fat and 20–30% for proteins [36,37]. In healthy subjects in energy balance with a mixed diet, DIT represents about 10% of daily total ingested energy [35]. One of the determinants of DIT is insulin sensitivity [38]. Insulin-sensitive individuals have a more pronounced thermic effect of food, whereas the most insulin-resistant individuals have negligible effects [38,39]. Furthermore, food temperature might influence EE. The intake of food or drinks cooler than core body temperature might elicit an increase in EE due to energy required for heating it up to body temperature [40]. Findings from this study have, however, been contested [41,42].

Each of these three components of EE is subject to regulation and can vary considerably from day to day and person to person [2]. However, in line with the first law of thermodynamics, when an individual ingests more energy than it expends, a positive energy balance develops and excess energy is stored as high-energy molecules. Sixty to 80% of excess energy is converted into triglycerides.

Small daily aberrations from a neutral energy balance can, over time, contribute to significant weight gain. When energy intake exceeds EE by merely 20 kcal/day (the equivalent of 1 tsp. of sugar) a person would gain approximately 1 kg of fat per year (≈20 kg over 2 decades) [2]. Remarkably, many adults maintain constant body weight for long periods of time with little conscious efforts. This is partly explained by adaptations in EE (RMR and NEAT) in conditions of over- and underfeeding [8]. In physiological conditions, complex regulatory systems constantly monitor energy status, and an appropriate response in feeding and EE is orchestrated.

2.1. Energy Expenditure in Obesity

The contribution of reduced EE in the development of obesity has been controversial. Historically, it was believed that obesity was associated with "slow metabolism" due to lower RMR, AEE, and/or DIT contributing to a positive energy balance and subsequent weight gain [30]. Nonetheless, studies conducted over the past three decades have reported that absolute EE in obese individuals is in fact higher compared to their lean counterparts [43–49].

RMR is positively associated with weight [43–48,50,51] with reported differences up to 800 kcal/day when comparing individuals with a BMI >50 (RMR = 2157 kcal/day) to lean individuals (RMR = 1331 kcal/day) [47]. In obesity, increases in fat mass occur concurrently with increases in FFM [45]. After correcting RMR for FFM the higher RMR found in obesity is blunted [45,48,50,52–54]. Notably, most studies adjusted RMR simply by dividing it by FFM [43–45,48,50,52,54].

In addition, obesity is associated with a higher absolute AEE [43,46,48,53]. Differences between lean and obese individuals diminish after adjusting for FFM [43,46,48,53]; indicating that the obese state itself does not intrinsically alter AEE. Nevertheless, obesity is associated with increased sedentary behavior [55], which negatively influences (adjusted) AEE. Therefore, sedentary lifestyle is contributing to positive energy balance and, consequently, obesity.

Studies examining the relationship between DIT and obesity yield inconsistent results. Some described lower DIT in obesity [55–60], whereas others found no difference in DIT between lean and obese individuals [61–63]. Investigating the influence of obesity on DIT is complex due to many confounding variables that may introduce bias, such as the level of physical activity [64] and insulin-resistance [38,39,65]. In addition, obesity is associated with a prolonged absorptive state, which confounds the duration of DIT measurement. Altogether the evidence is insufficient to support the theory of an altered DIT in obesity. Fig. 1 shows variations of energy expenditure between lean and obese individuals.

In summary, studies do not support hypotheses of altered RMR and/or DIT in obesity, but lower NEAT and EAT may contribute to body weight gain. Emerging obesity phenotypes such as normal-weight obesity [51] and sarcopenic obesity [66] might be accompanied with an altered EE compared to lean individuals or obese without sarcopenia.

2.2. Effect of Caloric Restriction on Energy Expenditure

Calorie-restriction strategies induce weight loss and are, therefore, commonly applied in the treatment of obesity [67]. With (intentional) weight loss, energy requirements fall and compensatory decreases in all components of EE occur [67–70] to match this lower energy intake. Twenty percent weight loss results in a 325–480 kcal/day reduction of EE [71]. The loss of FFM during weight loss largely contributes to lower EE. However, during caloric restriction, the process of metabolic adaptation induces a disproportional decrease in RMR. This metabolic adaptation can account for a reduction in RMR up to 500 kcal daily [72]. The mechanism explaining this phenomenon is still unclear in humans but probably involves the hypothalamus-pituitary-thyroid axis and lower sympathetic activity [73]. This reduction in EE comes along with increases in hunger [70] further challenging adherence to caloric restriction in the absence of (permanent) behavioral change. The lack of success in long-term weight loss maintenance [74] suggests that most individuals are not able to match the lower EE with lower food intake mandatory to sustain weight loss.

2.3. Metabolic Efficiency

The inter-individual energy required to maintain body weight in individuals with similar physical characteristics can vary widely [30]. Differences in metabolic efficiency might explain this variability and play a role in the susceptibility to weight gain.

The transformation of (energy embedded in) carbohydrates and lipids into actual task performances requires two consecutive metabolic processes [2]. First, nutrients are oxidized to yield adenosine triphosphate (ATP) that serves as metabolic currency [2]. Second, ATP is utilized into actual task performances, e.g., vital body functions and physical activity [2]. In line with the second law of thermodynamics,

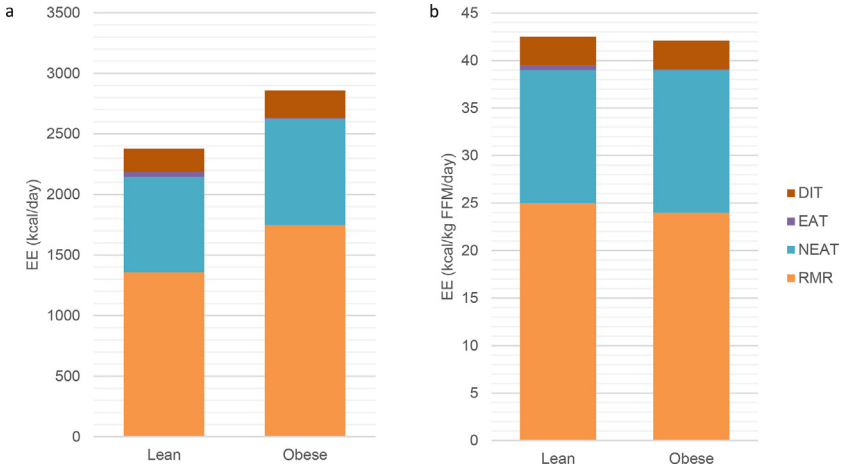

Fig. 1. Components of total EE in lean and obese individuals unadjusted (a) and adjusted (b) for FFM. In absolute terms, obese individuals have higher EE than lean individuals [43–47,61]. The main compartments contributing to these differences in EE are RMR and NEAT [43–47,61]. After adjusting for FFM these differences are blunted [43,44,47,49,61,62]. The contribution of EAT in the obese state is (close to) zero [43]. Average findings from all references are used for this graph. DIT: diet-induced thermogenesis; EAT: exercise-related activity thermogenesis; FFM: free-fat mass; NEAT: non-exercise-related activity thermogenesis; RMR: resting metabolic rate.

both processes involve heat production [2]. Metabolic efficiency refers to the proportion of ATP vs heat production derived from a given task performance [75].

Ability to dispose part of excess energy as heat decreases the ability to store excess energy as fat and, thus, prevents weight gain [75]. Low metabolic efficiency implies an increase in heat production at the expense of ATP production (and conversion into triglycerides) [76]. Enhanced metabolic efficiency has been reported to contribute to obesity [76]. In rodents, metabolic efficiency is also increased during caloric restriction [73]. The variability in metabolic efficiency is in part genetically determined [77].

2.4. Sympathetic Nervous System Activity

The sympathetic nervous system (SNS), is involved in homeostatic control, and altered SNS activity has been suggested to contribute to obesity. Fasting reduces SNS activity [78,79], whereas feeding, especially carbohydrate overfeeding, is associated with increased SNS activity [80–82]. Leptin and insulin, among others, are likely involved in mediating these effects on SNS activity [83,84]. These findings suggest that the SNS is involved in the restoration of energy balance [85].

A causal relationship between body weight gain and SNS activity in humans remains difficult to establish because the lack of long term longitudinal studies. Tataranni et al. showed a negative correlation between urinary norepinephrine (NE) excretion as a measure of SNS activity and subsequent weight gain over 3 years in Pima Indians and NE excretion explained 10–15% of the weight gain [86]. Surprisingly, at baseline, NE excretion did not correlate with 24 h energy expenditure (or respiratory quotient) suggesting that the correlation between baseline NE excretion and subsequent weight gain was through an increase in food intake which was not assessed in that study.

The SNS has other specific effects on metabolism: it promotes pancreatic insulin release [87], adipose tissue lipolysis [88], skeletal muscle glucose uptake [89], and hepatic glucose mobilization [90]. Reduced SNS-mediated adipose tissue lipolysis has been suggested to contribute to enhanced lipid accumulation and, consequently, excess weight [91]. It has also been hypothesized that altered regulation of core temperature by the SNS predisposes to weight gain (lower core temperature, lower RMR). Studies in lean and obese humans, however, show contradicting results: obesity has been associated with normal [92], decreased [93,94], or increased [95,96] SNS activity. In addition, lean and obese individuals do not differ in core temperature during inactivity, activity, or eating [97], and all changes in REE or DIT upon overfeeding were dependent on changes in FFM [98]. Overall, the SNS is an important regulator of systemic metabolism, and affects energy balance and long-term body weight. Its precise role (and therapeutic potential) in the current obesity epidemic, however, remains to be determined [99].

3. Energy Intake

Animals, unlike plants, obtain all energy requirements from ingested food and drink. To balance energy intake and expenditure, there are complex systems that regulate eating behavior [100]. These systems operate at the crossroads of several brain circuits and receive input from peripheral signals that relay information on nutritional state [101]. However, illustrated by the current obesity epidemic, these systems are highly vulnerable to disturbances that unbalance energy intake and expenditure.

The two major systems that control food intake are often referred to as the homeostatic and hedonic pathways [102]. The homeostatic pathway stimulates eating behavior when energy stores are low. The hypothalamus and brainstem have been identified as its centers. Here, central and peripheral signals, including circulating concentrations of nutrients, gastrointestinal hormones, insulin, leptin, and vagal afferents, are integrated to mediate feelings of hunger vs satiety and adjust food intake. The hedonic, or reward-based, pathway adds another layer of control and may override the homeostatic system [102].

By mediating the rewarding and motivational aspects of food intake, the hedonic system can support energy homeostasis during periods of relative energy deficiency, but also increase the intake of highly palatable food during periods of relative energy sufficiency [103]. During evolution, high sensitivity for food cues was probably beneficial, because this increased the chance of successful food foraging and survival [104]. However, in the current obesogenic environment, increased motivation for food intake may be less advantageous [104]. Obesity likely develops when the hedonic and homeostatic regulatory systems are out of balance [103]. Several neurotransmitter and brain circuit-related hypotheses have been postulated to explain the relative abundance of energy intake that causes obesity [70,100,103,105,106].

3.1. Neurotransmitters and Food Intake

3.1.1. Serotonin

Serotonin is an important neurotransmitter in the homeostatic pathway, and studies in animals and humans have shown that manipulation

of serotonin changes eating behavior [108,109]. Decreased serotonin signaling in the hypothalamus is hypothesized to contribute to obesity by impairing negative feedback from ingested energy on food intake, thus promoting overconsumption [107].

Serotonin is produced in the raphe nuclei of the brainstem and involved in the regulation of food intake via projections to multiple brain regions of the homeostatic and hedonic regulatory systems [108]. Most of the available evidence points to a model where increased serotonergic signaling is associated with decreased food intake, whereas decreased serotonergic signaling induces hyperphagia and weight gain [110]. The effect of serotonin on food intake is thought to be twofold. Serotonin is able to activate the anorexigenic α-melanocyte-stimulating hormone (α-MSH), a product of pro-opiomelanocortin (POMC) neurons, and inhibit the orexigenic neuropeptide Y (NPY) and Agouti-related peptide (AgRP) neurons located in the arcuate nucleus of the hypothalamus [111]. However, we note that this is a simplification of serotonergic reality and not all recent findings match this straightforward model [112]. Nevertheless, the importance of serotonin is also supported by in vivo human studies that use molecular neuroimaging, including positron emission tomography (PET) or single photon emission tomography (SPECT). Most of these indicate that human obesity is associated with decreased serotonergic signaling (for a review, see [113]), thereby supporting the human relevance of the hyposerotenergic theory of obesity development. In line, the serotonin 2c receptor agonist lorcarserin induces weight loss in obese humans [114].

3.1.2. Dopamine

Another explanation for the imbalance between homeostatic and hedonic regulation is postulated in the reward deficiency theory. This hypothesis states that decreased dopaminergic signaling, which normally relays the rewarding aspects of (food-related) stimuli, promotes the overconsumption of palatable food beyond homeostatic needs in order to compensate for lower reward sensations [121].

Recent advances in neurobiology have greatly enhanced our understanding of the neuronal and peripheral factors involved in eating behavior; for an overview of the functional organization of feeding circuits, we refer to the available literature [100,111,122]. Briefly, the hedonic system is headquartered in the striatum, with close connections to the hypothalamus and homeostatic system [123]. In animal models with reduced dopamine signaling through striatal D2 receptor knockdown, a phenotype of compulsive-like food seeking and obesity is observed [124]. In addition, in humans the presence of the A1 allele of the DRD2/ANKK1 Taq1A polymorphism, which is associated with lower dopamine D_2 receptor ($D_{2/3}R$) availability [125], increases the risk for the development of obesity [126]. There is also increasing evidence from human neuroimaging trials in support of reward deficiency. Recent fMRI data demonstrate reduced striatal activity in response to food consumption in obese compared to lean subjects [117,127]. In fact, reduced neuronal activation in the striatum upon food intake may be predictive of future weight gain, and this finding was particularly strong in individuals with the Taq1A A1 allele [127]. In accordance, PET and SPECT data show decreased striatal availability of the dopamine D_2 and D_3 receptor ($D_{2/3}R$) in obese vs lean individuals, although the correlations between BMI and $D_{2/3}R$ availability have not been consistent and the relationship is not necessarily linear [113]. Few molecular neuroimaging trials have assessed changes in $D_{2/3}R$ availability, which reflect dopamine release and receptor binding, in response to food-related stimuli, but the available data suggest that striatal dopamine release is impaired in obese humans [128,129]. Overall, these data are consistent with the hypothesis that reduced striatal dopamine signaling may drive people to overeat in compensation [127].

Another theory, which may in fact complement the reward deficiency hypothesis, postulates that overeating in obesity is caused by higher expectations of reward for food. This is supported by fMRI studies, where obese subjects had increased neuronal activation in brain regions of the cerebral reward system upon exposure to visual food cues or taste [130–135]. A combination of increased expectations of reward and reduced sensations of reward would surely prompt people to overeat.

3.2. Nutritional Feedback

Both the homeostatic and hedonic regulatory systems receive input from multiple signals that convey information on energy intake, current energy status, and long-term energy stores. These signals close the energy expenditure-intake feedback loop and are therefore essential for the maintenance of energy balance. Obesity is associated with several changes in nutritional feedback.

3.2.1. Taste and Smell

Taste is one of the first food intake-related signals to the homeostatic system [136]. Taste receptor cells are located in taste buds on the tongue [137], activated by molecules in food and drink [137], and linked to the brainstem and hypothalamus via gustatory sensory afferent neurons in the facial and glossopharyngeal nerves [136].

Studies on taste perception in obesity have produced mixed results [138]; overall, higher BMI seems to be associated with lower intensity of sweet, salt, and umami perception [139–141]. In addition, more recent data from animals [142] and humans [143,144] suggest that dietary fatty acids may produce their own gustatory sensations, i.e., the taste of fat [145]. In this light, decreased fatty acid chemoreception has been implicated in the development of obesity [146], although a recent meta-analysis of 7 trials did not reveal any differences in fatty acid taste detection between lean and obese subjects [144].

One mechanism for taste dysfunction, which was recently demonstrated in mice [147], implicates obesity-induced chronic low-grade inflammation in the reduction of taste bud abundance. This finding suggests that obesity precedes taste dysfunction, but it is likely not the only mechanism. Nevertheless, taste intensity does seem to be important. When healthy volunteers were randomly assigned to pharmacological inhibition of sweet taste perception (vs control), they developed a preference for food with higher sucrose content, i.e., more intense stimuli, suggesting that impaired sweet taste may contribute to increased sugar consumption [148]. Obesity may also be associated with changes in smell [140], but the directionality of this relationship is, as of yet, unclear. Interestingly, an acquired loss of olfactory function protects mice from becoming obese and promotes weight loss and insulin sensitivity in diet-induced obese (DIO) mice [149]. These effects were, surprisingly, not caused by a reduction in food intake, but were found to be mediated by SNS activity and adipose tissue thermogenesis, indicating a previously unknown link between the olfactory sense and metabolism.

3.2.2. Gastrointestinal Hormones

Gut hormones and peptides are well-known regulators of gastrointestinal motility and digestive function. In addition, it has become increasingly clear that hormones and peptides secreted by endocrine cells in the stomach, gut, and pancreas are important modulators of whole-body metabolism and food intake, thereby contributing to the control of energy balance [150]. Several gut hormones, secreted in response to fasting or exposure to ingested nutrients, affect eating behavior by promoting satiation or hunger, and their circulating concentrations have been shown to differ between lean and obese individuals [151].

Ghrelin, the only known orexigenic or hunger hormone, is primarily produced in the gastric fundus. Its levels go up during fasting and its secretion may be controlled by the sympathetic nervous system [152] and is suppressed postprandially, i.e., in response to nutrient intake [153]. Ghrelin stimulates appetite, promotes meal initiation, and has been implicated in the regulation of long-term energy balance [154]. Fasting ghrelin levels and BMI are negatively correlated, and human obesity is associated with reduced postprandial ghrelin suppression [155].

Anorexigenic intestinal hormones, including glucagon-like peptide 1 (GLP1), peptide YY (PYY), and cholecystokinin (CCK), are secreted in response to food intake or nutrient exposure and involved in, among others, digestion, insulin secretion and post-digestive metabolism, and satiety [150]. Meal consumption in obese humans is associated with delayed, reduced, or otherwise attenuated activity of anorexigenic hormones [156,157].

Perturbations in the suppression of ghrelin and/or rise of anorexigenic hormones may contribute to impaired homeostatic inhibition and reward deficiency; consequently, the gut hormones have been intensively investigated over the past few decades, but their precise role in the complex regulation of eating behavior and obesity development in humans – and their potential as therapeutic targets [158] – is not fully elucidated yet. Recently, clinical trials with GLP-1 analogues showed promising results on body weight regulation [159–161].

3.2.3. Leptin

Leptin is predominantly secreted by white adipose tissue. Circulating levels correlate with fat mass and represent a hormonal signal of body energy stores [162–165]. In individuals with more body fat, serum, plasma and cerebrospinal fluid leptin levels are elevated [165]. Leptin binds to its receptors, primarily relaying information on energy status [165–168], but also on acute energy availability [169–171]. In the hypothalamus, leptin mediates most of its actions [172–175]. Here, the activity of several hypothalamic neurons and expression of various orexigenic and anorexigenic neuropeptides are under its influence [168,176–180]. [181]. Briefly, leptin activates neurons that synthesize anorexigenic peptides, including POMC, and suppresses the activity of orexigenic neurons [166,174,175,182–185]. In addition, leptin counterbalances the effects of ghrelin [186,187]. Overall, in leptin-sensitive individuals, leptin signaling results in a decrease in food intake and an increase in energy expenditure to maintain the size of energy stores [188–193]. Conversely, low leptin levels augment food intake and suppress energy expenditure [188–193]. Despite elevated leptin levels, obesity is characterized by impaired leptin signaling, i.e., leptin resistance, which explains why leptin administration to most obese individuals is not effective [194]. Leptin resistance is thought to result from hypothalamic inflammation and gliosis [195–197], but many other mechanisms are involved. Mutations in genes encoding components of the leptin-melanocortin pathway result in early onset obesity (further described below) and subjects with these rare conditions benefit from therapy with leptin or melanocortin receptor 4 agonists [198,199].

3.2.4. Insulin

In addition to orchestrating postprandial metabolism, insulin also contributes significantly to nutritional feedback: its effects on the hypothalamus promote satiety [200], whereas it enhances dopamine release in the striatum, thereby signaling reward [201]. Obesity is characterized by insulin resistance, a condition that may also develop in the brain [202], suggesting that insulin-mediated nutritional feedback may be impaired in obesity. Indeed, insulin's effect on striatal dopamine dynamics was disturbed in rats fed a high fat high sucrose diet [203]. Whether insulin contributes to the development of overconsumption and thus obesity or facilitates reward-driven food intake in the setting of obesity is unknown. Interestingly, we have recently shown that striatal dopamine release promotes whole-body insulin sensitivity [204], indicating a bidirectional link between insulin action and the reward system. On the contrary, as insulin's peripheral, anabolic effects result in the depletion of circulating nutrients, peripheral insulin may indirectly stimulate food intake by a decrease in plasma glucose and free-fatty acid levels [205].

3.2.5. Cerebral Nutrient Sensing

Mice without sweet taste receptors still develop a preference for sucrose over non-caloric sweeteners [206], indicating that the reinforcing effects of sugar are not only attributed to taste. Circulating nutrients, now called post-absorptive nutrient signals [207], also provide nutritional feedback to the CNS. In mice, intragastric nutrient infusion, bypassing naso-oral chemoreception, induced striatal dopamine release depending on caloric value of the infusion [208]; in humans, it altered brainstem and hypothalamic neuronal activity [209,210]. Mechanisms underlying post-absorptive nutrient signaling remain to be elucidated, but emerging rodent data suggest that separate dopaminergic circuits are involved in chemoreceptive (olfactory, gustatory) vs post-absorptive (gut hormones, circulating nutrients) signals [207]. It is currently unknown how these steps in nutritional feedback are altered in human obesity, but one study, comparing obese to lean subjects, showed that the increase in cerebral ATP upon intravenous glucose infusion is diminished [211], indicating either impaired brain energy delivery or reduced ATP production, which may be one mechanism contributing to the “hungry brain”.

3.2.6. Gut Microbiota

Gut microbiota, often referred to as a separate metabolic organ [212], facilitate the digestion of dietary components, including those components that the innate digestive system cannot process. Gut microbiota thereby increase the efficiency of energy harvest from ingested nutrients [213], and it has been hypothesized that gut microbiota contribute to weight gain through this mechanism [214]. In addition, metabolites produced by gut microbiota and bacteria-derived components may modify systemic metabolism [215]. In mice, fecal transplantation from an obese to a lean animal causes weight gain and obesity, suggesting a causal role for microbiota in the development of obesity [214,216]. In humans several studies found differences in microbiome composition and diversity between lean and obese subjects [217–219], but these findings have not been consistent [220].

Studies in rodents show effect on homeostatic and hedonic control of food intake. However, so far, evidence supporting causality in humans is scarce [221]. For an overview on the role of gut microbiota in body weight regulation, we refer to ref.: [222].

3.3. Circadian Rhythms

Circadian clocks orchestrate all biological functions (from gene expression to apoptosis) in a rhythmic 24-hour periodicity. The central circadian clock is located in the CNS, specifically in the suprachiasmatic nucleus (SCN) of the hypothalamus [223,224]. Most metabolically active cells also have an internal, peripheral clock that enables tissues to regulate gene expression locally in an autonomic manner [225–228]. The central clock is primarily synchronized by afferent signals from the retina [229,230], but fine-tuned in response to other signals such as meal timing and food composition [231,232]. Peripheral clocks, in turn, are synchronized by signals from the SCN and have several mechanisms to influence metabolism, including circulating levels of hormones and metabolites. Circadian misalignment, i.e., disruption of the circadian rhythm, due to altered timing of food intake and diet composition can give rise to the development of metabolic disorders [233–235]. In animals, changes in the circadian rhythm are associated with changes in eating behavior and weight gain [236]. As a result, (night) shift workers are at greater risk of obesity and obesity-related disorders [237,238]. Modifying the time of feeding alone can significantly affect body weight [239,240].

3.4. Cause and Effect

Almost all human data on the homeostatic and hedonic system are derived from cross-sectional studies, which do not support conclusions on causality. It is still debated whether the described changes in obesity are the *result* of (long-term) obesity or *predispose* to a positive energy balance and weight gain. We have shown that serotonin transporter availability increases within six weeks of hypercaloric high-fat high-sugar snacking in lean adults, suggesting that cerebral effects of a

hypercaloric diet arise early and may contribute to the progression of weight gain [241]. This effect was not observed with other hypercaloric diets, indicating a role for diet composition in mediating these effects. Meal timing may be similarly important: obese subjects in a hypocaloric diet intervention study, who consumed most calories at breakfast, had increased thalamic serotonin and striatal dopamine transporter availability, whereas those, who consumed calories at dinner, had decreased availability of both transporters [242]. We have also shown that striatal D2/3R availability is reduced in obese women, but partially reversible after bariatric surgery-induced long-term weight loss [243]; this suggests that obesity may, in fact, cause the observed changes in the dopamine system. Evidently, longitudinal follow-up and controlled intervention trials are required to resolve the issue of causality, but the available evidence suggests it may, in fact, go both ways.

4. Genetic Causes of Obesity

4.1. Leptin-Melanocortin Pathway

As outlined above, the leptin-melanocortin pathway plays a pivotal role in food intake and energy balance. Leptin stimulates POMC neurons in the arcuate nucleus to produce a series of melanocortin peptides. The melanocortin α-MSH binds with high affinity to melanocortin 3 receptor (MC3R) and MC4R in the paraventricular nucleus [244,245]. These signaling pathways subsequently coordinate energy intake and expenditure [246,247]. Mutations in genes involved in the leptin-melanocortin tract have, to a greater or lesser extent, been associated with (childhood-onset) obesity.

First, patients with homozygous or compound heterozygous mutations in leptin have reduced leptin levels- and activity, or in case of homozygous/compound heterozygous mutations in the leptin receptor (LEPR) an impaired leptin receptor signaling ability, leading to obesity [248]. A leptin or *LEPR* mutation occurs in approximately 1–5% of the morbidly obese population [247,248]. Second, homozygous/compound heterozygous mutations of the *POMC* gene are associated with severe early-onset obesity, combined with features of adrenocorticotropin hormone (ACTH) deficiency, pale skin and red hair. The last two features are due to the role POMC plays in the determination of melanocytes [249]. Third, *MC4R* mutations in humans result in a phenotype of early onset obesity and hyperphagia [250]. Approximately 2–5% of the childhood-onset obesity cases are due to a heterozygous mutation of *MC4R*; making a *MC4R* mutation the most common cause of monogenic obesity [250–252]. Finally, heterozygous mutations in *MC3R* have been identified in humans with obesity, but the underlying mechanism is unclear. However, mice lacking the melanocortin 3 receptor show increased body fat and decreased FFM due to increased food efficiency and relative inactive behavior. This phenotype was more prominent on a high-fat diet [253,254].

Mutations in POMC-derived transcripts such as in the proprotein convertase subtilisin/kexin type 1 (PCSK1) inhibitor have also been associated with an obese phenotype. Patients with homozygous/compound heterozygous mutations in *PCSK1* suffer from obesity. This could be the result of impaired POMC processing, since similar phenotypic aspects, such as glucocorticoid deficiency, are also seen inpatients *POMC* mutations [247]. Other mutations in the leptin-melanocortin pathway, e.g., in the accessory proteins interacting with the melanocortin receptors, could also result in early onset obesity. Mice with disruption of the melanocortin-2 receptor accessory protein 2 (Mrap2), a modulator of the melanocortin 4 receptor, show an obese phenotype [255,256]. In human obesity, rare *MRAP2* variants have been identified, but their exact role in obesity has to be further explored.

In addition to these causes of monogenic obesity without intellectual deficit, where a variant in one gene is causing the phenotype, obesity can also be part of a syndrome, where obesity is associated with congenital malformations, dysmorphic features and/or intellectual deficits. Overviews of syndromic causes of obesity are provided in Tables 1 and 2, but will not be further elaborated in this review [257].

4.2. Polygenic Obesity

Monogenic causes of obesity are rare and account for approximately 7.3% of (severe) childhood-onset obesity [258]. In most individuals, however, genetic predisposition to obesity is expected to be polygenic, in which the phenotype is caused by the additional effect of variants in multiple genes. In 2007, common variants in specific parts of fat mass and obesity associated (FTO) gene were associated with a higher BMI in humans [259–262]. Subsequently, other polygenic variants were identified after large meta-analysis of genome wide association

Table 1
Obesity syndromes without intellectual disability.

Name syndrome or gene	Genetic defect	Inheritance	Main characteristics apart from obesity
ADCY3	Homozygous or compound heterozygous mutations in adenylate cyclase 3 (*ADCY3*)	Autosomal recessive	Severe obesity and hyperphagia. Anosmia (infrequently reported)
Alström syndrome	Homozygous or compound heterozygous mutations in ALMS1, centrosome and basal body associated protein (*ALMS1*)	Autosomal recessive	Retinitis pigmentosa, diabetes mellitus, hearing impairment
DYRK1B	Heterozygous mutations in dual-specificity tyrosine phosphorylation-regulated kinase 1B (*DYRK1B*)	Autosomal dominant	Abdominal obesity, metabolic syndrome
KSR2	Heterozygous mutations in kinase suppressor of ras 2 (*KSR2*)	Autosomal dominant	Mild hyperphagia, insulin resistance, reduced metabolic rate
LEP	Homozygous or compound heterozygous mutations in leptin (*LEP*)	Autosomal recessive	Hyperphagia, hypogonadotropic hypogonadism, hypothyroidism, frequent infections
LEPR	Homozygous or compound heterozygous mutations in leptin receptor (*LEPR*)	Severe: autosomal recessive	*Homozygous*: hypogonadotropic hypogonadism, hypothyroidism, growth hormone deficiency, frequent infections
MC4R	Homozygous or compound heterozygous mutations in melanocortin 4 receptor (*MC4R*) Heterozygous mutations in *MC4R*	Severe: autosomal recessive Moderate: autosomal dominant	Hyperphagia, accelerated linear growth (height and occipitofrontal circumference), hyperinsulinemia
MRAP2[a]	Heterozygous mutations in melanocortin 2 receptor accessory protein 2 (*MRAP2*)	Autosomal dominant	Hyperphagia
PCSK1[a]	Homozygous or compound heterozygous mutations in proprotein convertase subtilisin/kexin type 1 (*PCSK1*) Heterozygous mutations in *PCSK1*	Severe: autosomal recessive Moderate: autosomal dominant	Neonatal diarrhea, hypothyroidism, adrenal insufficiency, diabetes insipidus
POMC	Homozygous or compound heterozygous mutations in proopiomelanocortin (*POMC*) Heterozygous mutations in *POMC*	Severe: autosomal recessive Moderate: autosomal dominant	*Homozygous*: red hair, pale skin, adrenal insufficiency Hyperphagia
SH2B1	Loss of function mutations in SH2B adaptor protein 1 (*SH2B1*) or as part of the 220-kb 16p11.2 deletion	Autosomal dominant	Hyperphagia, hyperinsulinemia, behavioral problems

[a] Future conformational studies needed.

Table 2
Obesity syndromes with intellectual disability.

Name syndrome or gene	Genetic defect	Inheritance	Main characteristics apart from obesity
16p11.2 deletion syndrome	Microdeletion chromosome 16p11.2 (220 kb, 593 kb, or 1.7 Mb deletion)	Autosomal dominant	Autism, large occipitofrontal circumference, epilepsy (20%)
Albright hereditary osteodystrophy	Heterozygous mutations in GNAS complex locus (*GNAS*) - Maternally: pseudohypoparathyroidism type IA - Paternally: pseudopseudohypoparathyroidism	Autosomal dominant	Short stature, round face, skeletal defects, multi-hormone resistance in pseudohypoparathyroidism type IA. Sometimes mild intellectual disability
Bardet-Biedl syndrome	Homozygous or compound heterozygous mutations in >20 Bardet-Biedl associated genes	Autosomal recessive	Polydactyly, retinal defects, renal defects, hypogonadism
BDNF	Heterozygous mutations in or chromosomal rearrangements affecting brain-derived neurotrophic factor (*BDNF*)	Autosomal dominant	Hyperphagia, ADHD, memory problems, impaired pain sensation
Borjeson-Forssman-Lehmann syndrome	Heterozygous mutations in PHD finger protein 6 (*PHF6*)	X-linked recessive/dominant	Severe intellectual disability, epilepsy, hypogonadism, microcephaly, coarse facial features. In females mild clinical features
Carpenter syndrome	Homozygous mutations in RAB23, member Ras oncogene family (*RAB23*)	Autosomal recessive	Acrocephaly, syndactyly of hands and feet, congenital heart defects, growth retardation, hypogenitalism
Carpenter syndrome 2	Homozygous or compound heterozygous mutations in multiple EGF like domains 8 (*MEGF8*)	Autosomal recessive	Craniosynostosis, polysyndactyly hands and feet, defective lateralization
CPE	Homozygous mutations in carboxypeptidase E (*CPE*)	Autosomal recessive	Hypogonadism, developmental delay (one patient reported)
Cohen	Homozygous or compound heterozygous mutations in *VPS13B*	Autosomal recessive	Hypotonia and failure to thrive in childhood, microcephaly, visual impairment, neutropenia, prominent central incisors/uplifted upper lip
Fragile X syndrome	Mutation in fragile X mental retardation 1 (*FMR1*), trinucleotide (CGG)n repeat expansion >200	X-linked dominant	Long face, large ears, prominent jaw, macro-orchidism, autism. Moderate to severe intellectual disability. Pre-mutations can lead to a fragile X tremor/ataxia phenotype
Kleefstra syndrome 1	Heterozygous deletion at chromosome 9q34.3 or heterozygous intragenic euchromatic histone lysine methyltransferase 1 (*EHMT1*)	Autosomal dominant	Severe intellectual disability, epilepsy, hypotonia, brachycephaly and typical facial features
mUPD14	Maternal Uniparental Disomy of Chromosome 14 (imprinting disorder)	Isolated cases, low recurrence risk	Neonatal hypotonia and feeding difficulties, pre-cocious puberty, short stature, mild intellectual disability
MYT1L (Mental retardation, autosomal dominant 39)	Heterozygous mutations in myelin transcription factor 1-like (*MYT1L*) or chromosomal rearrangements at 2p25.3	Autosomal dominant	Autism, speech delay, behavioral problems
NTRK2	Heterozygous mutations in neurotrophic receptor tyrosine kinase 2 (*NTRK2*)	Autosomal dominant	Hyperphagia, developmental delay
Prader-Willi syndrome	Absence of expression of imprinted genes in the paternally derived Prader-Willi critical region (paternal deletion, mUPD15, or imprinting defect)	Depending on underlying mechanism	Neonatal hypotonia and feeding difficulties. Later in life hyperphagia. Hypogonadism, short stature, characteristic facial features
Schaaf-Yang syndrome	Heterozygous mutations of mage family member L2 (*MAGEL2*) on the paternal allele	Autosomal dominant	Neonatal hypotonia and feeding problems (Prader-Willi like), behavioral abnormalities. Mild contractures to fetal akinesia
SIM1	Heterozygous mutations in *SIM1* and chromosomal rearrangements affecting *SIM1*	Autosomal dominant	Autism, behavioral problems
SINO syndrome (spastic paraplegia, intellectual disability, nystagmus, obesity)	Heterozygous mutation in kinase D interacting substrate 220 (*KIDINS220*)	Autosomal dominant	Spastic paraplegia, ophthalmologic defects, typical facial features, macrocephaly and tall stature in first year of life
Smith-Magenis syndrome	17p11.2 interstitial deletion or, less frequently, heterozygous mutations in retinoic acid induced 1 (*RAI1*)	Autosomal dominant	The obesity occurs mostly in patients with *RAI1* mutations
Spastic paraplegia 11	Homozygous or compound heterozygous mutations in SPG11, spatacsin vesicle trafficking associated (*SPG11*)	Autosomal recessive	Progressive spastic paraplegia, learning disabilities with or without decline, peripheral neuropathy
TUB	Homozygous mutations TUB	Autosomal recessive	Retinal defects, hearing impairment
Turner syndrome	Complete or partial loss of one X chromosome (with or without mosaicism)	Mostly not inherited, only partial deletions of the X chromosome can be inherited from a parent	Short stature, premature ovarian failure, primary hypogonadism, webbed neck, low posterior hair line. Most have normal intelligence, but learning and behavioral problems are possible

studies (GWAS) for BMI. Altogether, these studies made it possible to develop and apply genetic risk scores for the determination of the role of polygenic variants in obesity [263]. Domingue and coworkers showed that these genetic risk scores are positively correlated with BMI [262]. Notably, due to the small effect size of each single gene variant, most GWA studies are underpowered. Therefore, definite conclusions cannot be drawn from these studies. Hence, future research needs to focus on larger patient cohorts to further elucidate genetic variances in obesity prone genes.

4.3. Epigenetics

Epigenetic programming in sperm cells, oocytes, and embryos plays an important role in the regulation of growth and metabolism. This can be seen in genetic obesity syndromes caused by imprinting defects, such as Prader-Willi and Temple syndrome. In both syndromes, imprinting disorders result in a phenotype characterized by short stature and neonatal feeding problems followed by hyperphagia and obesity. Exposure to environmental factors can also cause obesity through epigenetic mechanisms. This was first shown in the Dutch Hunger Winter study, where people prenatally exposed to famine during the second world war had significant epigenetic changes in the IGF2 gene compared to their unexposed siblings [264]. Recent advances in the role of epigenetics in obesity are described in: ref. [265].

4.4. Genetic Obesity: Implementation in Clinical Care

Knowledge of genetic obesity syndromes and the molecular mechanisms underlying these syndromes is crucial for reproductive decision making, reducing obesity stigma, and the discovery of novel

mechanism-based pharmacologic treatments. Diagnosing genetic obesity has already led to personalized therapies for obesity. The most illustrative example is the successful treatment with subcutaneous leptin injections in patients with congenital leptin deficiency. In these patients, leptin therapy has also shown to be effective for other associated symptoms, such as preventing recurrent infections and inducing puberty [198]. Notably, leptin therapy in patients without (congenital) leptin deficiency has no effect [194]. The newest therapeutic agent in genetic obesity is the MC4R-agonist setmelanotide. This drug showed promising results in two patients with proopiomelanocortin deficiency with a weight reduction of 20.5 kg after 12 weeks in the first and 51 kg after 42 weeks in the second patient [199]. A follow-up study, using setmelanotide in patients with leptin receptor deficiency described similar results [266]. Finally, clustered regularly interspaced short palindromic repeats (CRISPR) and its associated protein (Cas) genome editing techniques have potential to treat genetic (obesity) syndromes. Developments in this technique are therefore closely monitored by all experts in the field of genetics.

5. Conclusions

Significant advances in understanding the pathophysiological mechanisms in the development and maintenance of obesity have been made. Obesity seems to be the result of impaired brain circuits and neuroendocrine feedback associated with pathological overeating and physical inactivity. A small proportion of the obese population is affected by a monogenetic mutation causative of obesity. Additionally, many obesity susceptibility genes have been identified in GWA studies. Despite recent advances in knowledge on the development and progress of obesity, our understanding of its etiology and pathophysiology is still incomplete. In particular, longitudinal follow-up and controlled intervention trials are required to resolve issues of causality. Nevertheless, due to the accelerating effects of obesity on metabolic outcomes and cancer, it has the potential to be pernicious to mankind if preventive measures and/or effective therapies are not realized.

Declarations of Interest

None.

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