The obesity treatment dilemma: why dieting is both the answer and the problem? A mechanistic overview

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Abstract

Restricted-calorie diets are the most worldwide used treatments for obesity. Although such strategies are based on the first law of thermodynamics, the real life clinical practice demonstrates that the observed weight losses are divergent from those theoretically predicted. Loosely adherence to recommendations is one of the main causes for the limited efficacy of dieting, but many additional factors can be involved in the hurdles to weight loss. According to the second law of thermodynamics any restriction in dietary energy intake results in energy sparing with a diminution in the basal metabolic rate and a concomitant loss in the lean body mass. This “thrifty” energetic adaptation is associated with a progressive reduction in the difference between levels of energy intake and expenditure, thus resulting in a drastic fall in weight loss rates on the medium and long-term regardless of the dietary carbohydrate/fat ratio. This loss of efficacy is aggravated by the misadaptation of the production and action of anti-obesity hormones such as leptin. During the latest past decades the discovery of changes in the gut microbiota of obese people referred to as “obese dysbiosis” has raised the question as to whether these alterations can participate to diet-resistance. Combined with the behavioral and psychological barriers to low-calorie diets, there is a broad physiologic spectrum of evidence indicating that weight loss is a hard challenge. Consequently, the answer would be primarily to prevent the development of obesity and at worst to avoid its ominous progression from metabolically healthy to unhealthy stages.

Key words: Barriers to weight loss; Obesity; Physiological misadaptations

Introduction

Temporal kinetics of weight loss in obese subjects treated with low-calorie diets is usually characterized by a relatively fast decline in body weight during the initial period after implementation of dieting [1-4]. After a few weeks the rate of weight loss becomes more gradual and finally after a few months the downward changes in body weight frequently cease [5] to be eventually replaced by upward drifts back toward the baseline weight [6]. Such disappointing outcomes are not only observed in obese people without diabetes but also in those suffering from prediabetes [7] or diabetes [8-10]. Several causes have been proposed for explaining such unfavourable weight loss patterns. It is now well recognized that the poor effectiveness or absence of success with restricted-calorie diets is mainly due to the failure of adherence to dietary prescription, a phenomenon that can rapidly occur in the time course of dieting and that usually increases over time [11-13]. In some cases a complete drop out from obesity treatment programs is observed. However behavioural dysfunction is not the unique explanatory factor and others are involved in such disappointing temporal kinetics of weight loss because it is well known that, even in persons exhibiting full compliance to the prescribed diet, the predicted weight loss should slow down on the medium-term with stabilization [4,5] or an eventual regain in body weight on the long-term [6]. Consequently, there arises the question as to whether low-calorie diets are associated with satisfactory results on the short-term but fail to exert such effects on the medium and/or long-term. The objective of the present review is to address this issue and to analyze the main factors that intervene for reducing and beyond for annihilating the rate of weight loss during dieting.

Thermodynamic causes

The energy metabolism in humans obeys to physics and chemistry principles that are governed by the 2 laws of thermodynamics [14-16]. According to the first law the energy balance should be set at an ideal level, while the second law explains that any change in energy intake or in the total energy of the body results in both changes of the free energy and entropy of the system. The free energy is mainly used for the development and renewal of body proteins i.e. of the cell body mass while the entropy is the energy released as heath to maintain the body temperature at its normal and stable level. As in obese people the energy balance and metabolic pathways are markedly dysregulated and subject to changes during periods of upward or downward weight fluctuations it seems of importance to briefly remind the main bases of the first and second laws of thermodynamics.

The first law of thermodynamics

In its simplest formulation this law can be expressed as: “the increment or decrement in the total energy stored in the body (ΔU) = Q – W” where Q and W correspond to the energy from dietary intakes and the overall energy expenditure, respectively [14]. In normal individuals with stable weight and healthy eating patterns, ΔU is equal to 0, which means that Q = W. Any weight gain over a more or less prolonged period is characterized by a positive energy imbalance (ΔU > 0) with Q > W. In contrast, any weight loss corresponds to negative decrements in the total stored energy (ΔU < 0), thus implying that Q is lower than W. According to this principle, and given the fact that any weight loss of 1 kg requires a negative imbalance of 7700 kcalories [17], a dietary regimen that reduces the average daily energy intake by 500 kcalories should result in a weekly energy loss of 3500 kcalories and thus in a corresponding body weight loss of 0.5 kg [2]. Unfortunately, this optimistic theoretical calculation is contradicted by the results observed in real life where weight losses are usually less than half of the degree predicted from the energy deficit [2]. Two types of causative factors that will be further detailed can explain such discordances. The first one is mechanistic and corresponds to the energetic adaptation characterized by a progressive decline in energy expenditure during restricted- calorie diets [18-20]. The second cause is behavioural with a gradual fall in compliance to low-calorie diets that are always constraining in obese individuals and that require sustained efforts over prolonged periods [21].

In practice, the two quantities W and Q should be assessed in obese persons before the prescription of low-calorie diets and throughout periods of weight loss. The indirect calorimetry rationale based on the measurement of gas exchange, i.e. on whole body O_2 uptake and CO_2 release, is the most valuable method for quantifying the energy expenditure [14,16]. However, the relatively high cost of the equipment and the constraints to maintain the hood or the canopy for monitoring the exhaled breath beyond several minutes are two main limiting factors for its routine clinical utilization although this method is usually available in many hospital settings provided that their ward units are sufficiently concerned by the investigation of metabolic and nutritional diseases. The body bioelectrical impedance can offer an alternative to the indirect calorimetry because this tool has the potency to estimate the basal (resting) metabolic rate from the fat free mass [22]. Despite intra-individual variability with respect to age, gender and ethnicity, it has been established that these two parameters are linearly and strongly positively correlated [23]. However, it should be noted that the basal metabolic rate has to be multiplied by a coefficient depending on the degree of physical activity for achieving a global assessment of the total energy expenditure W [24]. When the indirect calorimetry and/or body bioelectrical impedance are not available, it is still possible to use the Harris and Benedict [25] or Schofield [26] equations. Despite the evident imprecision of such equations at an individual level, both provide an estimate of the basal metabolic rate from several demographic (age and gender) or anthropometric characteristics of the subjects (height and weight). Considering now the dietary

energy intake Q its assessment requires the use of self-administered food questionnaire [27,28] but the accuracy of such food recalls remains highly questionable because many patients, especially those who are obese are well known to be under-reporters [29,30]. Therefore adequate reporting is always the exception and never the rule.

The second law of thermodynamics

Its formulation is more complex than that of the first law of thermodynamics but in simple words the statement is that under conditions of constant pressure and temperature a close system, which does not exchange with its environment, is characterized by its total internal energy also referred to as its enthalpy (H) that can be divided into two components [15,16]. The first one is namely called free energy (G), which is harnessed as chemical energy in ATP. For instance a large amount of ATPs is generated during the complete aerobic metabolism of glucose and fatty acids: 36 and 129 molecules of ATP are coupled with the overall oxidation (H_2O and CO_2 as end products) of each unit of glucose and palmitic acid (C16:0), respectively [31]. ATP molecules are further hydrolyzed to ADP for releasing the energy required for protein synthesis. The second component referred to as the entropy (S) of the system is unavailable for doing work and yielding structural chemical substrates. The entropy is only used for thermogenesis and further dispersed as heath. In an isolated system the equilibrium between these two types of energy is regulated by the Gibb's equation: $H = G + TS$ where T is the temperature of the system. In human beings, the system is open on the environment and the equation becomes $\Delta H = \Delta G + T\Delta S$ where the deltas (Δ) express the temporal changes (increments or decrements) of H(t), G(t) and S(t). As catabolic pathways are unavoidable in humans, the degree of disorder of the total energy dispersed as heath, i.e. of their entropy (S), should be steadily increasing at the expense of the free energy (G) and all the total internal energy should finally be converted to heat. Fortunately, human beings are exchanging with their environment and the heat is released out of the body while the free energy is continuously restored via the conversion of dietary nutrients to biochemical substrates including ATP at first step and structural proteins at end point. In other words humans are permanently struggling to maintain a constant G/S ratio between the biological order of organized structures (G) and the biological disorder of entropy (S). During weight loss and under restricted-calorie diets, all quantities ΔH, ΔG and ΔS that are usually equal to 0 become negative and, consequently, the absolute values of H, G and S decrease (figure 1). However as ΔG is more affected than ΔS, the G/S ratio diminishes. Therefore restricted- calorie diets are associated with two unavoidable clinical consequences: a reduction in the lean body mass with an average as high as 25% of the total weight loss [32], which further results in a decrease in the basal metabolic rate [33,34] (figure 1). As mentioned above the basal metabolic rate and the lean body mass are linearly and positively inter-correlated and

thus one can predict that any 10-kg loss in the lean body mass should mechanistically result in a decrement in the basal metabolic rate by approximately 200 kcalories per day [23]. This prediction has been confirmed by the results of longitudinal studies in which any 30-kg reduction of the total body weight was found to be associated with a decrement of the total energy expenditure (Δ= -570 kcal/day) assessed from the double labelled water method [18-20]. The latter disorder contributes to the subsequent loss of efficacy of low-calorie diets, even when subjects remain fully compliant to the dietary restriction [33]. For all these reasons, it is recommended to exert a tight follow-up on the temporal evolution of both the lean body mass and basal metabolic rate over periods of weight loss. Once again repeated bioelectrical impedance measurements at regular time intervals can provide useful assessments of both parameters. An easier way would be to use measurements of 24-h urine nitrogen output as biological marker of the actual dietary protein intake and therefore of the total energy intake/expenditure [35]. This is simply due to the fact that in most individuals who comply to balanced eating patterns between major macronutrients the energy consumed as dietary proteins represents one sixth of the total energy ingested by the subjects irrespective of their phenotypes [36]. Furthermore it is commonly admitted that the 24-h urinary excretion rate of creatinine provides an estimate of the muscle mass with the following equivalence: a 1000-mg daily excretion rate approximately reflects a muscle mass of 20 kg [37]. Reverting to more sophisticated methods for energy expenditure measurements such as the whole body direct calorimetry [14,38] or the use of the double labelled water methodology [38,39], both are usually only available at research settings.

Additional data on thermogenesis

Although the conventional treatment of obesity usually consists of hypocaloric diets whose main concept is based on the first law of thermodynamics, several interventional trials were conducted to establish whether the respective contributions of dietary carbohydrates, fats and proteins could have an impact on the magnitude and time course of weight loss [40-46]. Consequently, it is necessary to remind that meals induce a transient increase in energy expenditure, the so-called thermic effect of food. This postprandial thermogenesis occurs over a 3 to 6-hour period after the beginning of a meal and depends on the nature of ingested nutrients: 5 to 10% for carbohydrates, 3 to 4% for fats and as high as 20 to 30% for proteins [47,48]. According to these data high-protein diets were proposed and tested for treating overweight states [49,50] but the outcomes remained poorly convincing [42,51]. Despite these results there remains that in order to prevent an abnormal loss in lean body mass it is commonly acknowledged that low-calorie diets should at least contain 20 to 25% of the total energy intake as proteins, preferentially to the usual 15 to 17 per cent range needed in healthy adults, which corresponds to the recommended amount of 0.8 grams of proteins per kilogram of desirable body weight [52]. As in obese people there is still an intense debate about the most appropriate distribution

of dietary carbohydrates and fats among the remaining 75 to 80% of energy intake [42,43,46], it seems timely to gain a deeper insight into the metabolic costs generated by the utilization of dietary carbohydrates and fats [47]. As illustrated in figure 2a, the additional energy requirement for lipogenesis, i.e. for storage of fats into the adipose tissue, is low (4% of the total energy intake from dietary fats) when dietary fatty acids are directly transported and incorporated into fat cells after intestinal absorption. As the additional metabolic cost for the utilization of fatty acids in other tissues is approximately of 3% (figure 2a), the average thermic effect of dietary fat intake on the postprandial rise in energy expenditure is, as mentioned above, rather small ranging between 3 and 4% (with an average of 3.5%). Consequently, for an individual with a daily consumption of 80 grams, i.e. 720 kcalories, as fats the energy kept by the human body is approximately of 720 -[720 x 0.035] = 695 kcalories. In contrast, the additional metabolic costs of carbohydrate intakes are largely greater and depend on the metabolic pathway used for substrate travelling from the intestine to target tissues: utilization for glucogenesis in the liver and kidneys (12%), oxidation and utilization as fuel in peripheral tissues such as muscles (7%) and lipogenesis with metabolic conversion into fatty acids for subsequent storage in the adipose tissue (23%) (figure 2b). By weighing up the contributions of the different metabolic pathways the average overall additional metabolic costs of carbohydrates is estimated between 5 and 8% (with an average of 6.5%), thus indicating that for any amount of 720 kcalories, i.e. 180 grams consumed as dietary carbohydrates, the human body only retains 720 - [720 x 0.065] = 673 kcalories. Therefore the additional metabolic cost with carbohydrates (47 vs 25 kcalories) is two times greater than that observed with fats. The consequence should theoretically be that carbohydrate-enriched diets would be more appropriate for initiating and maintaining weight losses than those containing high proportions of fats. However there arises the question as to whether the observation of such small differences can be translated into practice when it comes to the nutritional management of obesity. The divergent results reported in the literature [42,43,46] strongly suggest that any type of diets should be successful at least in the short-term as long as subjects are compliant to restricted-calorie diets.

Hormonal causes: leptin, insulin resistance and the concept of metabolically healthy and unhealthy obesities

Energy balance is controlled by a large number of peptides secreted by the gut and adipose tissue [53-59]. These peptides regulate food intake and energy homeostasis by either stimulating or reducing the activity or synthesis of several neuropeptides mainly located in the hypothalamus [56,60,61]. Among

these pathways the circuit containing the neuropeptide Y (NPY) is considered to be a fundamental step for the action of peptides synthesized in the intestinal tract and adipose tissue [60,61]. Experiments in animals have clearly demonstrated that any increase in secretion and release of the NPY exerts an orexigenic effect and promotes energy intake. In contrast, any reduction in the secretion of the NPY results in an opposite effect and is associated with a hyporexic response [60,61]. This relatively simple view of the neuropeptide-signalling pathways in the hypothalamus should not occult the complexity of homeostasis feeding and regulation of energy expenditure at the brain level. However this rather elementary approach should be sufficient for demonstrating the inappropriateness of hormonal responses to food intake restriction and for explaining why this misadaptation can be a causative factor for the limited and even the absence of weight loss that are frequently observed in persons submitted to low-calorie diets [2,5-7].

At the front of the scene: the role of leptin and its misadaptation

After the encoding of its gene in mouse in 1994 [62], leptin was identified as an hormonal peptide secreted by adipocytes with circulating levels proportional to the whole body adipose tissue mass. However 20 years before its full discovery, parabiotic experiments in mice [63] have strongly suggested the existence of a satiety humoral factor capable of reducing food consumption (figures 3a and 3b). Using the technique of parabiosis with a large anastomosis of skins between either db/db or ob/ob mice (later known as leptin resistant [64] or leptin deficient mice [62], respectively) and normal partners the following results were observed. When parabiotic pairs of mutant (db/db, i.e. later identified as leptin resistant) with normal mice were produced it was observed that the normal partner rapidly lost weight and died from severe starvation within 50 days after surgery (figure 3a) whereas no abnormal changes were observed in the db/db partner [63]. From the results of this experiment, it was postulated that the db/db mutant produces an increased amount of a satiety factor (later identified as leptin), which is transported to the cerebral satiety centre of the normal partner in whom it completely shuts off the normal partner's eating drive [63]. Other experiments have established that parabiosis of mutant obese mice (ob/ob, later identified as genetic leptin deficient animals [62]) with normal partners did not result in starvation and death of the normal mice. In such experiments the rate of weight gain was drastically reduced in the ob/ob partners and a moderate weight gain was observed in the normal mice [63] (figure 3b). Consequently, it appears that the parabiosis of ob/ob with normal mice is a completely viable combination, not lethal for the normal partner. At the time of these observations if was suggested that ob/ob mice do not produce a sufficient amount of satiety factor (later identified as leptin) to turn off the normal partners eating drive, but that the regular hormonal satiety factor released by the normal partners decreases the rate of weight gain in ob/ob mice by stimulating the activity of the cerebral satiety centre of the obese partners. As mentioned above, 20

years after these pioneering studies that had predicted the existence of an adiposity-sensing pathway regulated by a circulating hormone and its cognate receptor located in the hypothalamus, it has been demonstrated that this regulatory loop of feeding and energy homeostasis was mediated by an adipocyte-peptide referred to as leptin through its inhibitory effect on the neuronal production of the NPY at hypothalamic sites [53-55]. Leptin profoundly inhibits food intake, decreases body weight and appears as one of the most powerful anti-obesity hormone. As leptin is released in direct proportion to the adipose tissue mass its plasma concentration is elevated in obese persons, the higher the weight excess the greater the circulating concentration [65]. This observation is the rule except in rarely encountered categories of obese persons who have a genetic defect in leptin production [66]. Reverting to the most frequent types of obesity, it has been demonstrated that leptin levels fall rapidly in response to fasting [65,67]. This decline contributes to limit the rate of weight loss and facilitates the weight regain by exerting a stimulatory effect on appetite and reducing the energy expenditure [68,69]. Consequently, it has been proposed to reverse this decline by testing the ability of leptin supplementations. Unfortunately such leptin replacements [70] failed or had limited effect to stimulate the rate of weight loss in typically obese individuals who usually have elevated leptin levels at baseline. Such disappointing results suggest that the poor outcomes of restricted-calorie diets, even when their efficacy should be theoretically stimulated with leptin injections, are not only due to the decline in leptin release from a progressively reduced-adipose tissue mass but also to leptin resistance with a decrease of its inhibitory activity on appetite at the human brain level [60,68,71,72]. These observations highlight the difficulties met when trying to comprehend the metabolic phenomena that are associated with the development of overweight /obesity states and subsequently with their resistance to food restriction. For instance, it is hard to know which proportion of leptin resistance is due to either acquired or inherited factors, respectively. Should the leptin resistance is mainly the consequence of acquired factors such as the overfeeding that precedes the development and accompanies the progression of overweight/obese states it is not clear whether such conditions can be reverted and how long it could last. From a general point of view it is highly likely that leptin resistance is as long to disappear as the duration of disappearance of insulin resistance observed in obese patients with type 2 diabetes [73]. In other words the pathophysiological features of obese persons without diabetes (absolute increase in leptin secretion, but with relative defect of leptin release unable to fully compensate the leptin resistance [68]) could be compared with the well-recognized characteristics observed in newly diagnosed patients with type 2 diabetes or at early stages of the disease: absolute increase in insulin secretion, but with relative deficiency of the endogenous insulin secretion, which remains unable to fully compensate the insulin resistance at the hepatic and peripheral tissue sites [73]. Irrespective of the pathophysiological mechanisms involved the practical consequence is that the combination of decreasing leptin secretion and increasing leptin resistance

during restricted-calorie diets reduces the efficacy of such measures and amplifies the discrepancy between observed and predicted weight loss.

Role of other hormonal factors

Besides hormonal signals such as the leptin released from the adipose tissue, several peptides secreted by the gastrointestinal tract participate to weight regulation [56-59,74]. To deliver a comprehensive message rather than to extensively describe the endless increasing categories of peripheral modulators of appetite, the present analysis is deliberately limited to longitudinal changes in ghrelin and glucagon-like peptide 1 (GLP-1) during periods of weight loss. The first one is acknowledged as a powerful stimulator of appetite [56,60,75,76] whilst the second exerts an inhibitory effect [59,74,77], a property taken as advantage for the obesity pharmacotherapy with GLP-1 receptor agonists [78]. Surprisingly and unfortunately it has been demonstrated that diet-induced weight losses are associated with increased and decreased plasma levels of ghrelin and GLP-1, respectively [67]. Therefore it appears that weight loss induces a gastrointestinal response that counteracts the beneficial effects of low-calorie diets by increasing the release of circulating mediators that encourage the desire to eat (e.g. the ghrelin) and by reducing the secretion of those that facilitate weight losses (e.g. the GLP-1) through their action on the brain structures involved in the control of food intake [56,60,76]. Although the present analysis is limited to two intestinal mediators these observations highlight the misadaptation of hormonal responses to diet-induced weight loss and the difficulties encountered by overweight obese patients who wish to lose weight and who are permanently struggling against adverse hormonal signals that increase the activity of brain areas involved in the food intake decision-making and reward aspects of eating behaviour.

Role of insulin resistance and the concept of metabolically "healthy and unhealthy" adipose tissues

The "friendly" earlier stages of adipose tissue

The first main function of adipose tissue is devoted to energy storage in the form of triacylglycerols that are secondarily hydrolyzed and released as non-esterified fatty acids (NEFA) during periods of fasting and hypoinsulinaemia [79]. This function aimed at achieving the normal energy homeostasis in non-obese individuals corresponds also to the presence of a "metabolically healthy adipose tissue", a characteristic still observed during the earlier stages of human obesity [80,81]. In such individuals the adipose tissue mass can undergoes periods of expansion, stability or reduction and shows a metabolic

flexibility that allows adaptation to sudden periods of feeding changes and fasting. Unfortunately several metabolic abnormalities can evolve from this transient period of satisfactory regulation.

The ominous progression towards a "metabolically unhealthy" adipose tissue

The maintenance of adipose tissue within a relatively stable state is dependent on a normal vascularisation, which is required for the production of mature adipocytes from mesenchymental stem cells throughout a process that includes an intermediary step characterized by the presence of preadipocytes [82]. At maturity end point, adipose cells are represented by white, beige and brown adipocytes [81]. Even though these phenotypes differ with respect to their mitochondrial content, they have the capacity of exchanging metabolic functions between themselves [81], with the primary role being attributed to fat storage for white cells and thermogenesis for beige or brown adipocytes [83]. As illustrated in figure 4 the progressive decline in vascularisation and the subsequent hypoxia of adipose tissue with individuals' ageing can be followed by a remodelling characterized by the development of abnormalities in fat mass such as an infiltration by macrophages, neutrophilic, mast and eosinophilic cells with eventually a further progression towards fibrosis [81,84,85]. This type of reaction with proinflammatory and fibrotic cells can be detected by measuring the slight elevation of low-grade inflammation biomarkers such as the C-Reactive Protein (CRP) [86,87]. A large variety of adipokins (the interleukin-6, TNFα, resistin and others) [84,85,88] that are released from these inflammatory cells contribute to trigger or enhance the insulin resistance [73], one of the main characteristics in persons with a never disrupted expansion of adipose tissue mass. The insulin sensitivity in obese people is also dependent on the production of adiponectin, an adipocyte-derived factor [89,90]. For instance it has been established that high plasma adiponectin levels correlate with improved insulin sensitivity [89-91]. In addition adiponectin levels are relatively preserved and even increased at earlier stages of obesity, i.e. in metabolically healthy obese people, whilst in "dystrophic obesity" the secretion of this peptide significantly falls [92]. Bringing all these observations together it becomes easy to understand why in metabolically unhealthy obesity the insulin sensitivity of liver and peripheral tissues can be markedly altered with several adverse outcomes such as the onset of type 2 diabetes [93]. As insulin resistance mechanistically results in hyperinsulinaemia [73] and as insulin inhibits the activity of some intra-adipocyte enzymes such as the hormone-sensitive lipase [94], which normally stimulates the hydrolysis of triacylglycerols in fat cells, it is highly likely that the hyperinsulinaemia of insulin resistant states observed in obese people, particularly in those who have been obese for many years, serves as amplifying factor for limiting weight losses during restricted-calorie diets [95].

One of the conclusions arising from these observations is that the transition from metabolically healthy to unhealthy obesity [81] is of major concern and should be avoided. Therefore one main recommendation is to intervene as early as possible in the long-term evolution of obesity to prevent at an individual level the transition to later stages where dietary measures are poorly efficient. At this stage the patient can become candidate to alternative therapeutic strategies such as pharmacotherapies and/or metabolic surgery [11,96-98].

Gut dysbiosis in obesity: Interplay between nature and nurture

The human gut microbiota is viewed as an ecosystem of trillions of micro-organisms distributed into more than 70 bacterial communities that are clustered into 3 main subsets [99]. Each individual possesses a specific gut microbiota with a balanced partition between bacterial species [100]. The concept of "dysbiosis" has emerged when scientists started to question the association of some clinical disorders with sustained imbalance between gut bacterial communities [101]. For instance it was recognized that the gut microbiota of obese and lean subjects are different, thus leading to the definition of a new entity referred to as "obese dysbiosis" [102]. During the latest past decade, an increasing number of studies have attempted to address several issues concerning this condition. The first question is to know whether this abnormal gut microbiota pattern is inherited resulting from nature or acquired under the influence of dietary factors, i.e. the "environmental nurture". Secondly, should the "obese dysbiosis" is mainly due to the environment, there arises the question as to whether these acquired changes are self-maintaining and/or aggravating factors throughout the evolution of overweight/obese states.

The role of nature

As mentioned above the specific microbiota of each human being is associated with its individual "metagenome" based on a number of genes as high as 150 times the host genome [99]. However at an individual level the gut microbiota is characterized by its flexibility around a central core, thus explaining its intra-individual adaptation to several factors [103]. Many observations suggest that gut bacterial phenotypes are only poorly driven by "nature", the most demonstrative argument being given by differences found in humans and mice between microbiota of homozygous twins [104].

The role of nurture: what we see

Compared with the marginal role of "nature", "nurture" seems to be a key player in the "dysbiosis" of obese people. Interventional trials consisting to modify the nutritional model and to reduce the dietary energy intake indicate that eating patterns modulate the microbiota composition [99]. Additional

arguments for this hypothesis were provided by the finding of differences in microbiota composition between obese and lean subjects and by the results of observational and clinical studies published during the two latest past decades. For instance, experiments of microbiota transfection from obese or lean mice to axenic animals have led to the concept of a specific transmissible microbiota phenotype in obese [104]. However diverging results were observed from studies aimed at defining one single "obese phenotype" combining a smaller diversity in bacterial communities with modifications in the Bacteroidetes/Firmicutes ratio [102]. In normal weight subjects, the bacterial harvest from energy dietary intake to the overall metabolism is increased or decreased according to whether the Firmicutes or Bacteroidetes species are relatively deficient or preponderant [105]. Obese subjects with deficient microbiota resulting from inappropriate food intake exhibit "unfriendly" metabolic profiles with a reduction in insulin sensitivity and a state of low-grade inflammation [106]. Weight loss in obese adolescents was associated with an increased diversity of microbiota, the higher the weight loss the greater this favourable phenotype [107]. In addition, persisting alterations in the microbiota after one year of restricted-calorie diet are predictors for both smaller weight loss and less improvement in metabolic baseline disorders [108]. This large spectrum of beneficial effects on the microbiota was also found after either bariatric surgery with an increase in the Bacteriodetes /Provella ratio [109] or after transfection of the microbiota from normal weight to obese subjects [110].

The role of nurture: what we try to comprehend

Microbiota composition regulates body weight and metabolic rates through complex mechanisms that remain somewhat hypothetic [111]. Bacterial species are involved in energy harvesting from non-digestible polysaccharides. This mechanism whose participation can be as high as 10% of daily energy requirements could explain the rates of weight loss or regain, which are less or more pronounced, respectively, when obese subjects are submitted to different types of low-calorie diets [105,112]. Short-chain fatty acids such as those released during the fermentation process of non-digestible products act as signalling substrates for enhancing the synthesis and storage of fats and subsequently for deteriorating the insulin sensitivity. The dysbiosis reduces the oxidation rate of fatty acids in liver and muscles by inhibiting the cyclic AMP and thus by inducing an excessive storage of fatty acids. In addition the dysbiosis modifies the intestinal barrier permeability and contributes to initiate a low-grade inflammatory state that in turn facilitates the onset of insulin resistance. Finally, the microbiota can alter the production of biliary acid metabolites that are involved in the energy regulation and activity of satiety centres by modulating the signals arising from and delivered by intestinal hormonal peptides [113].

Potential applications of microbiota in clinical practice

In obesity, restricted - calorie diets induce short-term changes in the microbiota that can be reverted within a period of a few months. The microbiota impact on weight loss kinetics has been investigated when low-carbohydrate or low-fat diets were implemented in overweight subjects [114]. At month 3 weight losses were similar but microbiota compositions were found to be different with increases in Proteobacterial species, Bacteroidetes and Firmicutes versus decreases in Actinobacterial species and Firmicutes on low-carbohydrate versus low-fat diets, respectively. Reverting to baseline status was progressively observed over a 6 to 12-month period, thus suggesting microbiota resilience due to a feedback impact independent on amounts and types of energy intakes. In this latter study the composition of the initial microbiota failed to predict the magnitude of weight loss [115]. Relapse to obesogenic microbiota patterns after transient improvement could facilitate weight regain even during dieting, but this question has never been fully addressed in humans. In programs of induced-weight gain with dietary cycling consisting of sequential periods with high fat and low-calorie contents, it has been established that weight regain was faster and greater when the forthcoming high-fat sequence had been re- implemented [116]. In addition post diet microbiota phenotypes accelerate weight regain and relapse towards metabolic disorders. The transfer of such phenotypes to axenic mice was responsible for an abnormally high level of weight gain, thus suggesting a causative-effect link between the microbiota composition resulting from a high-fat energy diet and the weight regain following restricted-calorie diets. Such results seem to indicate that in subjects submitted to hypocaloric diets any manipulation of the microbiota is able to prevent or delay weight regain, but unfortunately in humans there is no evidence for the appropriateness of using microbiota analyses for predicting weight outcomes. In the future targeting the microbiota might be a complementary measure to individualize the treatment of obese people provided that we gain further insight into our knowledge on how the microbiota and its response to nature and nurture intervene in weight regulation [117].

Behavioural and psychological barriers to low calorie diets

Long-term self-motivation and family support are two key prerequisites for promoting successful weight loss. Psychological vulnerability is a common feature in obesity, which is due to several factors including poor global self-esteem, negative impact of social stigmatization and failure to correctly handle eating impulsiveness [118]. All these abnormalities result in situations where obese people are struggling against psychological stress, which in turn facilitates uncontrolled and emotional feeding disorders that aggravate weight excess. A bidirectional relationship has been described between obesity and mental health. Despite compelling evidence for beneficial somatic outcomes of weight loss there are less data concerning potential improvements of mental health. Poorly realistic recommendations on weight control are at risk of aggravating the stigmatization of obese people,

inducing behavioural eating disorders and enhancing symptoms of psychological distress especially when the targets of dietary interventions remain uncompleted [119]. In addition, high stress levels can be associated with weight gain as a result from a combination of increased energy intake with reduced physical activity. Such a situation is encountered after perceived stress following health - harming periods [120]. In contrast, a satisfactory psychological profile improves outcomes of weight management [121]. As the individual's psychological feature is one of the main predictors of weight loss and/or stabilization, due consideration should be given to it [122]. Contrarily to usual disseminated beliefs and according to data provided by a meta-analysis including several randomized controlled trials [123] plus one prospective study [124] examining the relationships between depression and obesity, weight loss programs seem to be devoid of any harmful effects on stress and anxiety perception. Relatively discordant results, but with neutral trends when considered as a whole, were observed in studies evaluating the psychological impact of low calorie diets [125]. In contrast progressive reductions in the rate of weight loss add anxiety and are at risk of inducing hedonic hunger and uncontrolled weight regain. Hedonic eating frequently alleviates the unhappiness feeling that results from diets, but can be also a subsequent risk factor of stress with undesirable effects [126]. Behavioural approaches may address this problem by stimulating the patient's motivation for and compliance to therapeutic changes in lifestyle and thus by allowing an appropriate response to the concern of wellbeing and management of associated psychopathologies such as anxiety and depression. Familial positive empathic and tolerant attitudes contribute to the effectiveness of dietary programs designed for losing weight with a particular mention for children and adolescents, who are dependent on parental food purchasing, preparation and availability, and who should be encouraged to start or increase physical exercise [127]. The professional environment is also a factor that can interfere with the long-term effectiveness of dieting in people exhibiting eating stereotypes such as convivial breaks, business meals or in those who exert professional occupations at increased risk of poor compliance to diets: people working in restaurants, workers exerting strong physical activity, business travellers or night shift workers. Vulnerable psychological profiles, unfavourable familial environments, poorly motivating professional occupations that hamper appropriate changes in lifestyle, are considered to be potential causative factors for weight loss failures.

Loss of compliance to dietary measures

Adherence to dietary measures is of great importance irrespective of the type of diet. The relationship between self-reporting of dietary compliance and weight loss is independent on the type of low-calorie diet [21]. Adherence during periods of weight loss is a predictor of weight stabilization over the 2 forthcoming years. In compliant subjects the averaged weight regain is limited to 50% compared with

an average of 90% in those who are poorly compliant [42,128]. Detecting a poor compliance during the initial period of dieting is predictive of weak results on the long term. By modelling the energy intake and expenditure it has been shown that poor compliance is the main determinant for weight plateau at month 6 [129]. Consequently, it should be pointed out that it is more appropriate to reinforce the compliance to diet than to intervene on its nutrient content, and therefore a particular attention should be given to socio behavioural conditions at the time of implementation of dietary measures.

Strategies used for improving adherence to diet

The desire to eat is a compensatory response that occurs during low-calorie diets and triggers weight regain [130,131]. Ketogenic low-carbohydrate containing diets have been proposed to improve adherence because high circulating levels of ketone bodies released from the hepatic oxidation of free fatty acids are associated with better tolerance to very low calorie diets (VLCDs) [132,133]. However this option is relatively disappointing because it is difficult to achieve such sustained energetic restrictions even though this approach accelerates the rate of weight loss during the initial period and can serve as "starter"[134]. The adherence to diet depends also on the magnitude of the gradient between the energy level of the prescribed diet and the habitual patient's consumption [42]. This observation was confirmed by the fact that the adherence score was improved in users of Mediterranean diets [135], because such regimens better fit with the average healthy eating patterns [52]. Food diaries are useful for improving compliance to diets. A systematic review assessing the importance of self-monitoring in weight management has shown that the higher the frequency of dietary self -reporting the greater the improvements in body weight [136]. Such monitoring is a reliable marker for the over-time maintenance of dietary changes even though servings are usually under-assessed. Household units and tables on composition of food are useful for putting recommendations into practice. In addition reshaping eating habits on the long-term necessitates a high quality formulation of dietary intakes and a participation to structured educational programs. For improving the patient's motivation and avoiding weight rebounds weight loss plans should include visits at regular time-intervals and healthcare professionals can implement additional individualized therapeutic strategies such as dietary manipulations aimed at increasing satiety with the use of high-fibre foods [137], mealtime structured plans and methods based on patient's empowerment or behavioural psychotherapy [11-13,138]. Nevertheless dietary manipulations are a subject of an endless debate because there is no evidence for the timeliness of modifying the respective contributions of macronutrients [40-46]. Therefore after decades of unfruitful attempts the main conclusion remains that weight loss is dependent on the adherence to calorie-restriction and on its intensity and duration [139,140].

Physical activity as adjuvant therapy

Due to its multiple metabolic impacts [141,142] physical exercise is an important component for weight loss. Adherence to exercise programs is one of the predictor for the effectiveness and durability of a restricted-calorie diet [143,144]. The intensity, duration, frequency and type of physical activity should be carefully adapted to the patient's health and physical capacities but also to his/her preferences. For instance, it should be reminded that in some individuals the recommendation to starting or increasing a physical activity creates more displeasure and constraints than changes in eating habits. Nor do we think physical exercise feasible in all obese persons even though it is well known that the combination of restricted-calorie diets with regular sessions of exercise reduces the risk for weight regain. However it must be noted that exercise alone is not sufficient for losing weight because the neurochemical mechanisms that regulate eating behaviour exert a compensatory effect on the thermic cost of exercise [145].

Conclusion

In summary it appears that losing weight is a hard challenge because all thermodynamic, neurochemical and endocrine systems respond to low-calorie diets and other therapeutic measures by counteracting their potential benefits. In other words the best treatment of obesity is preventive and each individual should adopt as early as possible a healthy eating pattern in order to avoid the development of excess weight because this clinical condition becomes less and less reversible with increasing duration of the disease and advancing patient's age. In the present review we have attempted to explain firstly why the "theory" helps to comprehend that reductions in body weight remain always possible, but also why the "practice" shows that in many situations the "theory" is poorly working, despite the optimistic, but unfortunately fake messages broadcasted by different medias or delivered by people who abusively claim to be nutritionists. When we combine "theory" and "practice" we understand what we see but in practice we see that nothing works as theoretically predicted.

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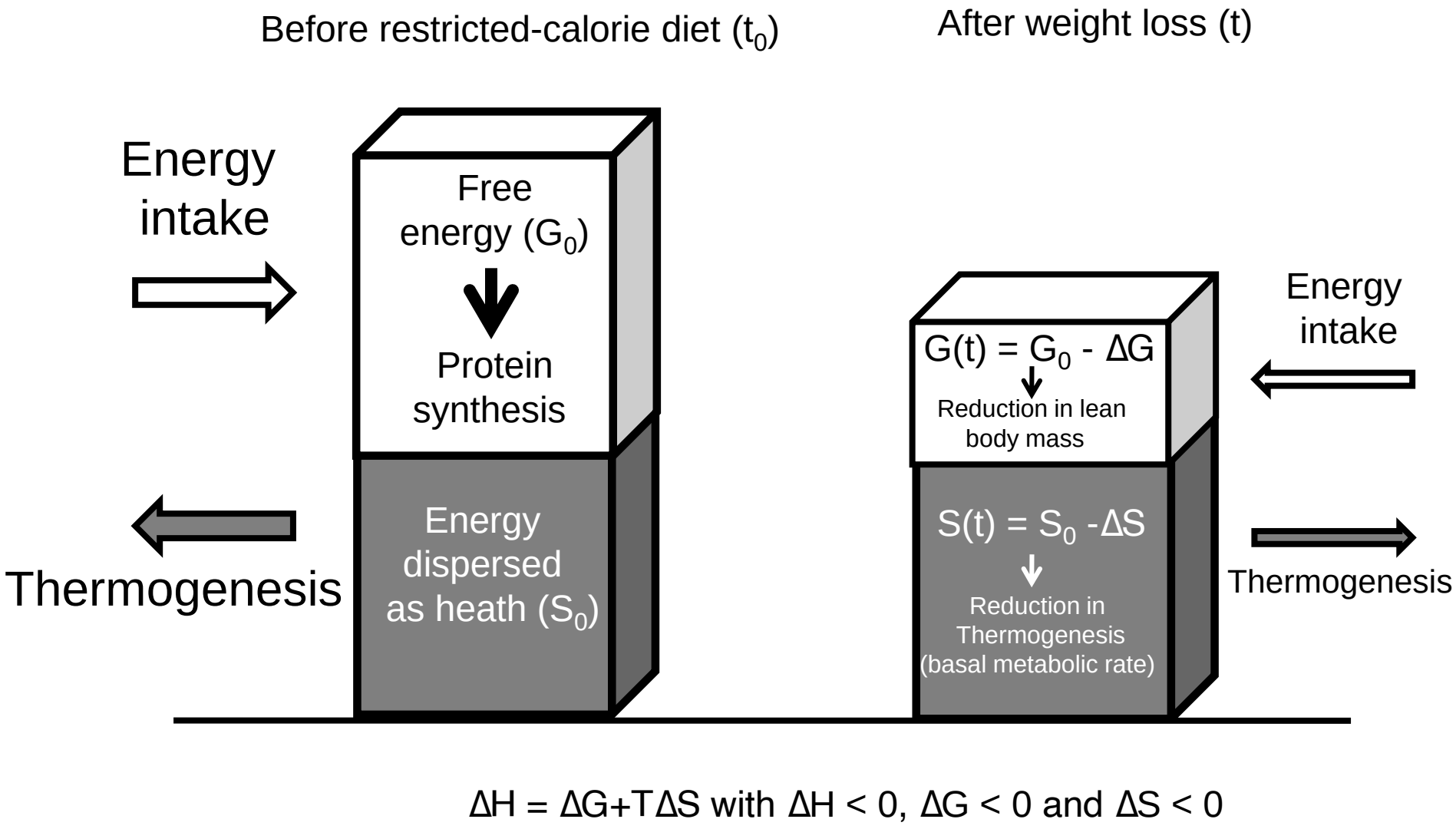
Legends of figures

Figure 1: Evolution of total energy (enthalpy, H), free energy (G) and entropy (S) during low-caloric diets. G is defined as the chemical energy mainly in the form of ATP that can be used for work, protein synthesis, i.e. for the preservation of lean body mass. S is the energy dispersed as heath. During restricted-calorie diets and accompanying weight losses, diminutions of G ($\Delta G < 0$) and S ($\Delta S < 0$) result in reductions of lean body mass and basal metabolic rate, respectively. A decrement in the G/S ratio is usually observed because ΔG is greater than ΔS, explaining why the loss in lean body mass is proportionally more pronounced than that of total body weight.

Figure 2: Schematic description of metabolic costs (thermic effects) of dietary fats (figure 2a) and carbohydrates (CHO) (figure 2b) according to whether food intakes are used for storage or for other purposes: physical activity, preservation and renewal of body substrates or maintenance of body temperature at a stable level. As a whole the thermic effects of carbohydrates (CHO) and fats are not significantly different, thus explaining why manipulations of the CHO/fat ratio during food restriction does not play a key role on weight outcomes.

Figure 3: Illustration of the impact of large parabiosis between db/db mice (genetically leptin resistant) (figure 3a) or ob/ob mice (genetically leptin deficient) (figure 3b) and normal partners. Twenty years before the discovery of leptin (an adipocyte-secreted peptide) these experiments have suggested the existence of a satiety factor (S-) released from the adipose tissue to turn off the appetite by exerting its effect on brain structures involved in the homeostasis of feeding and energy expenditure.

Figure 4: Schematic description of the two types of obesity individualized according to whether they are “metabolically healthy or unhealthy”. The latter type is characterized by an infiltration of the adipose tissue by proinflammatory cells and the release of adipokins, which both create a low-grade inflammation with elevated CRP levels and insulin resistance



$\Delta H = \Delta G + T\Delta S$ with $\Delta H < 0$, $\Delta G < 0$ and $\Delta S < 0$

Fig 2a

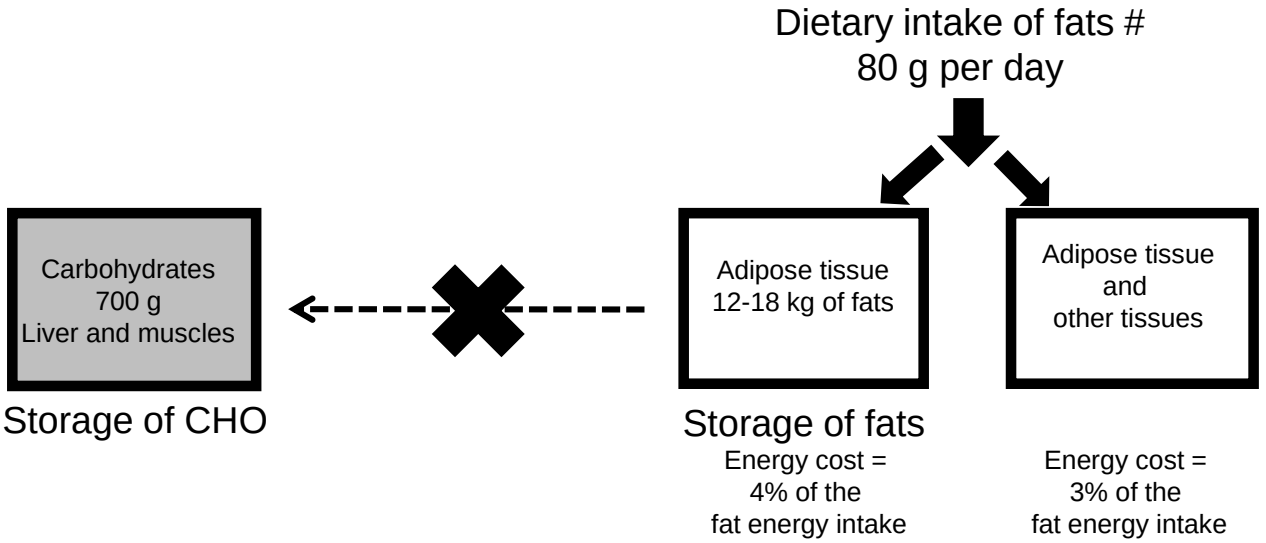
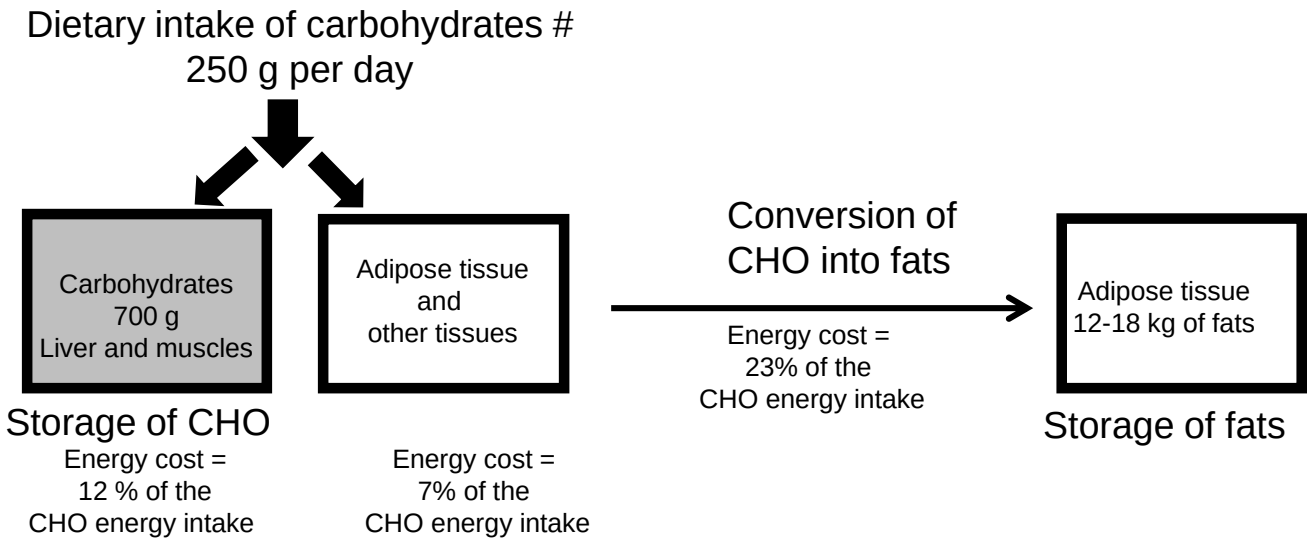
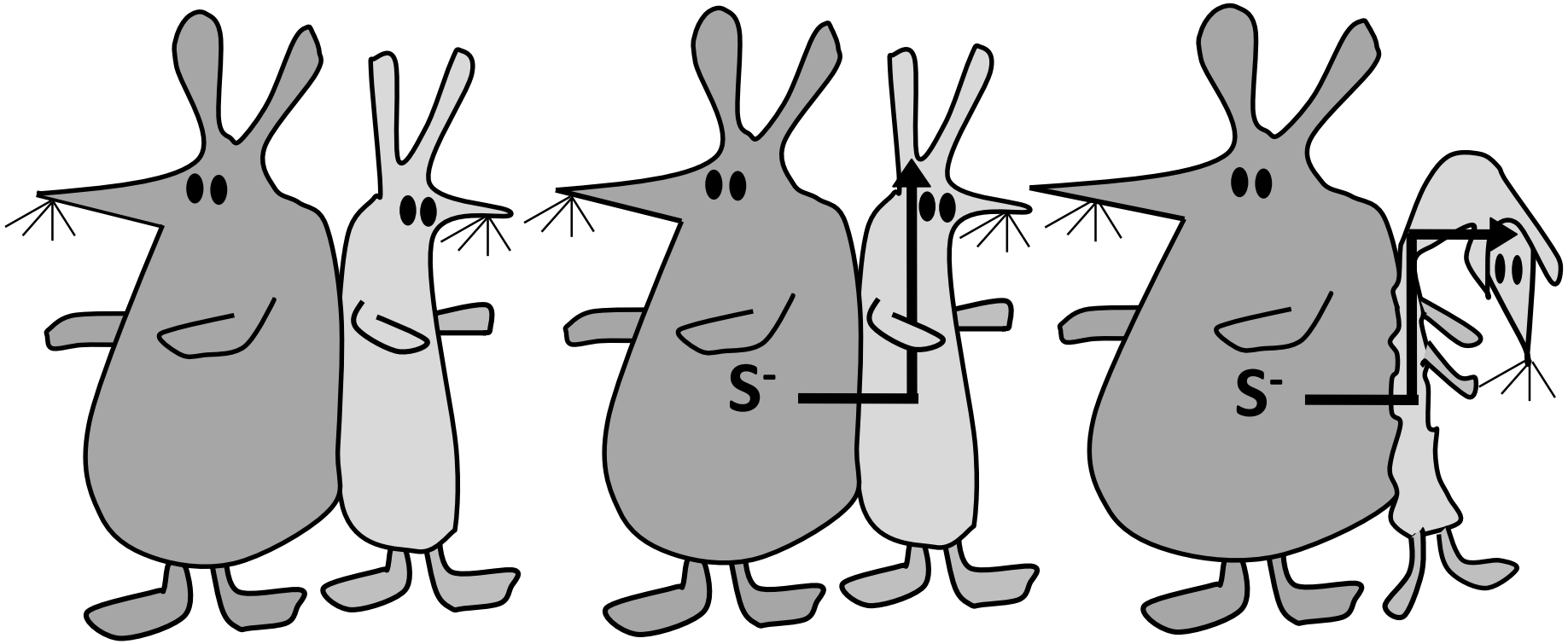

Dietary intake of fats #
80 g per day
Carbohydrates
700 g
Liver and muscles
Adipose tissue
12-18 kg of fats
Adipose tissue
and
other tissues
Storage of CHO
Storage of fats
Energy cost =
4% of the
fat energy intake
Energy cost =
3% of the
fat energy intake

Fig 2b


Dietary intake of carbohydrates #
250 g per day
Carbohydrates
700 g
Liver and muscles
Adipose tissue
and
other tissues
Conversion of
CHO into fats
Energy cost =
23% of the
CHO energy intake
Adipose tissue
12-18 kg of fats
Storage of CHO
Energy cost =
12 % of the
CHO energy intake
Energy cost =
7% of the
CHO energy intake
Storage of fats

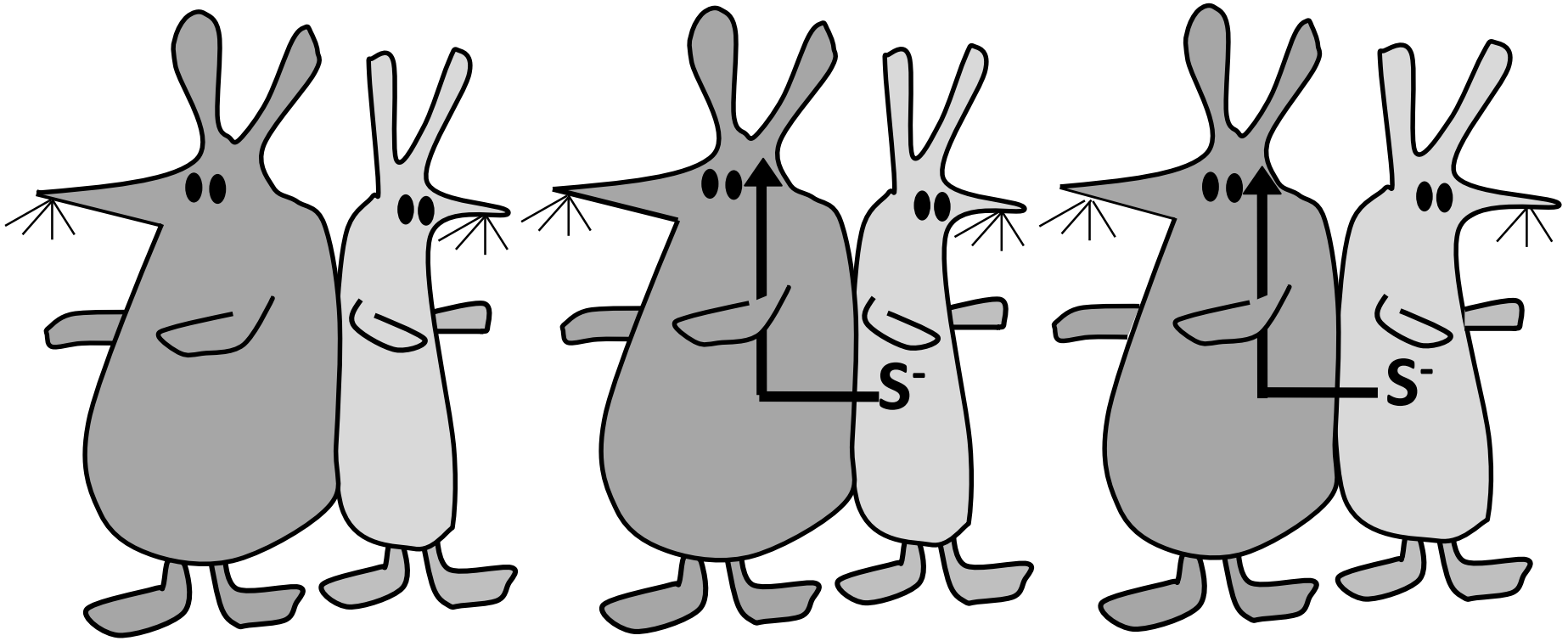
Parabiosis



db/db mouse

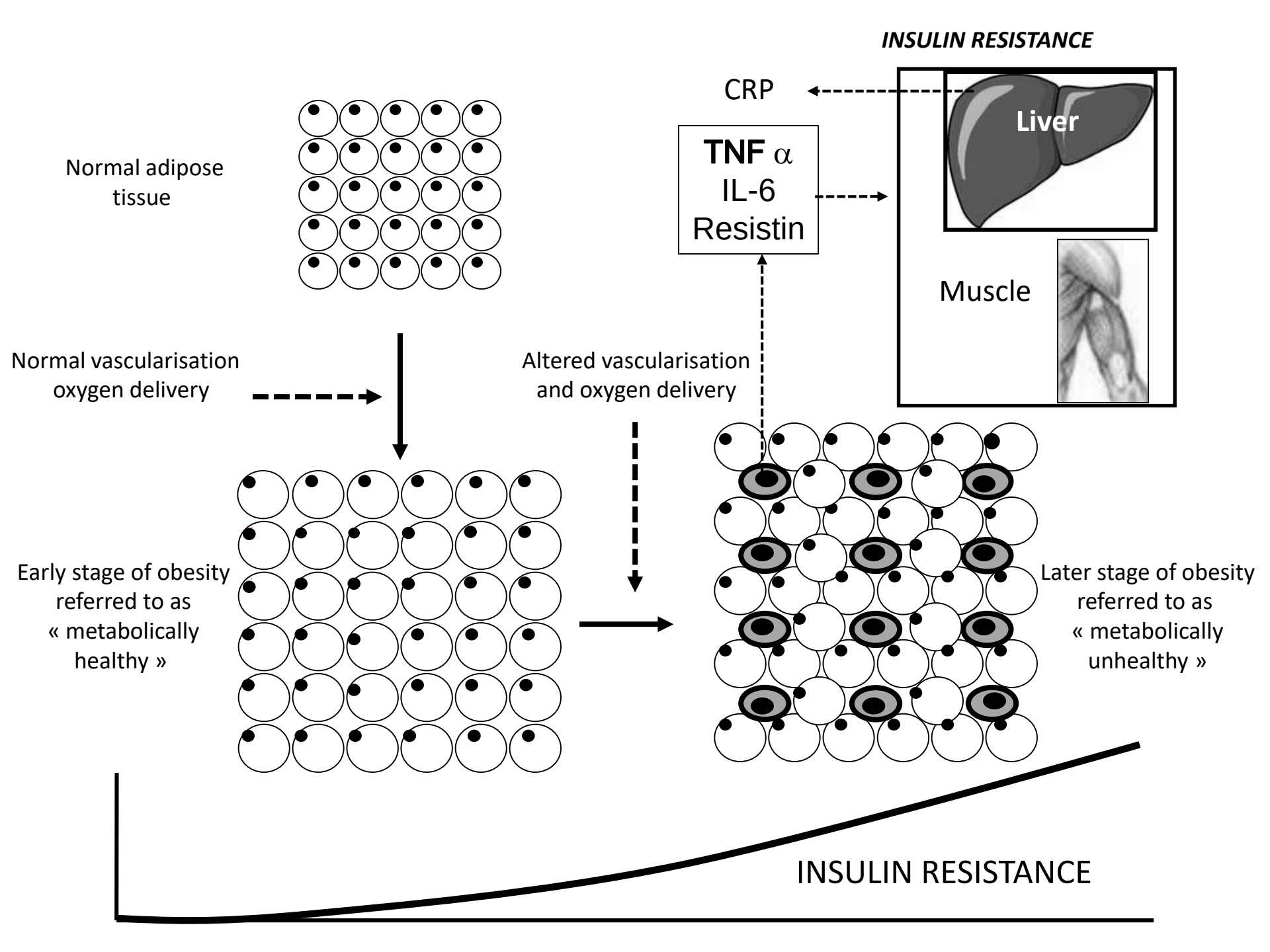
Normal partner

Parabiosis



ob/ob mouse

Normal partner


INSULIN RESISTANCE
CRP
TNF α
IL-6
Resistin
Liver
Muscle
Normal adipose tissue
Normal vascularisation oxygen delivery
Altered vascularisation and oxygen delivery
Early stage of obesity referred to as « metabolically healthy »
Later stage of obesity referred to as « metabolically unhealthy »
INSULIN RESISTANCE