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INTERACTION BETWEEN ADIPOSE TISSUE AND PHYSICAL ACTIVITY IN THE REGULATION OF BODY WEIGHT: A CONCEPTUAL NARRATIVE REVIEW

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ABSTRACT

The modern obesity pandemic is characterized by difficulty in achieving and maintaining weight loss. This suggests the existence of a physiological control mechanism to maintain body mass. However, this same mechanism did not prevent obesity pandemic. The aim of this review is to explain this conundrum. Online searches of Google Scholar, PubMed, and Scopus were conducted. The main variable under physiological control is not a fixed body/fat mass but balance between energy intake and expenditure. The expenditure includes resting metabolic rate, physical activity related energy expenditure and thermic effect of food. Increased energy expenditure triggers increased energy intake to match expenditure levels and counters any weight loss. This matching of energy input and output can happen at any body/fat mass. In other words, body/fat mass can settle at any level with energy intake matched to expenditure; the so-called settling point mechanism. The particular body/fat mass settling point is determined by the availability of energy and degree of expenditure enabled by the environment. The modern environment with abundance of nutrients and motorized work has been termed obesogenic environment. It facilitates higher body mass and hence increased resting metabolic rate energy expenditure to support the increased body mass; this triggers more energy intake and thus more mass gain in a positive feedback vicious cycle. In conclusion, shifting emphasis away from body mass control to energy balance allows one to explain both the modern obesity pandemic as well as why it is so difficult to achieve and maintain weight loss.

Keywords: Adipose tissue, Energy expenditure, Physical inactivity, Obesity, Narrative review

INTRODUCTION

Body weights appear stable over time (Speakman *et al*., 2011). This leads to a notion of body weight set-point maintained by homeostatic control mechanisms much like blood sugar or body temperature. The lean body mass (bone and skeletal muscle) changes little in adults and so changes in adult body weight are attributed to changes in body fat; thus body weight set-point control is the same as body fat set-point control or lipostatic theory (Speakman *et al*., 2011).

A major criticism of set-point theory of body fat is the presence of obesity in modern societies; if body fat is tightly regulated why do we witness rising obesity rates? Additionally, lipostatic theory could not also explain the increase in adiposity associated with aging (Speakman *et al*., 2011; Berthoud *et al*., 2020; Blundell *et al*., 2020).

The aim of this review is to review an extension of the body/fat mass set point theory to account for the rising obesity rates in modern times while still accounting for difficulty experienced in achieving and maintaining weight loss.

MATERIALS AND METHODS

Online searches of Google Scholar, PubMed, and Scopus were conducted using keywords: "adipose tissue", "adiposity", "physical activity", "energy intake", "energy expenditure", "energy balance", "weight loss" and "obesity". Boolean operators "AND" and "OR" were used to combine the search words during the database search.

RESULTS AND DISCUSSION

Body/fat mass set-point mechanism

Like all other negative control mechanisms, lipostatic mechanism (Figure 1) has a sensor, which detects changes in body fatness, an integrative center represented by the neuronal nuclei located in the arcuate nucleus and effector responses of energy intake (EI) and energy expenditure (EI) (Speakman *et al*., 2011).

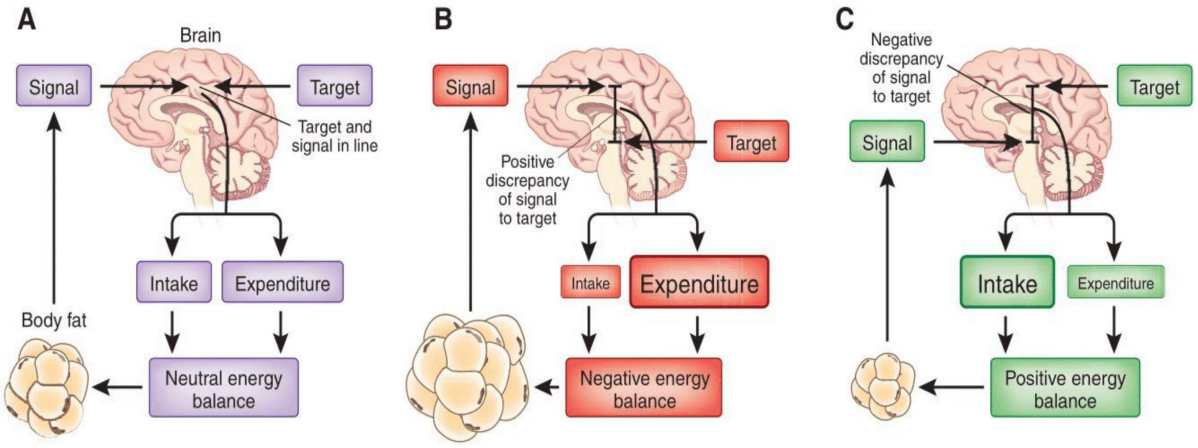


Figure 1: Lipostatic Set-Point Mechanisms of Body Weight Regulation. Source: Speakman et al., (2011)

The lipid sensor is the protein hormone leptin secreted by adipocytes; the hormone is secreted in proportion to the total body fat. A higher leptin secretion signifies higher fat mass and a lower leptin secretion signifies lower fat mass (Berthoud *et al*., 2020; Speakman *et al*., 2011). Monogenic mutations in the leptin gene *ob* leads to uncontrolled obesity in mouse models (Blundell *et al*., 2020). Higher fat mass and higher leptin levels (Figure 1C) leads to downregulation of the orexigenic neuropeptides such as neuropeptide Y (NPY) and agouti-related protein (AgRP) and upregulation of anorexigenic peptides such as proopiomelanocortin (POMC) and alpha melanocyte-stimulating hormone (alpha-MSH) in the arcuate nucleus of the hypothalamus to inhibit food intake and to increase beta-oxidation of fatty acids and increase total energy expenditure (Berthoud *et al*., 2020; Speakman *et al*., 2011). The combined effects of decreased energy intake and increased energy expenditure leads to a negative energy balance and loss of fat mass (Berthoud et al., 2020). Conversely, fat loss (Figure 1B) leads to lower leptin levels and lower anorexigenic impulses and lower energy expenditure; the increased food intake and decreased energy expenditure leads to a state of positive energy balance and gain of fat mass (Berthoud *et al*., 2020; Hopkins & Blundell, 2017; Speakman *et al*., 2011).

Energy expenditure is a prime driver of energy intake

Leptin mediates its negative feedback mechanism of fat mass control through energy intake and expenditure. However, energy input/output is also determined by factors independent and at times antagonistic to leptin effects. To describe these other factors we need to first the question: what creates the drive to eat? The obvious answer is energy expenditure necessary to maintain life (including of resting metabolism, thermogenesis and physical activity) (Blundell *et al*., 2020; Hopkins & Blundell, 2017; Stubbs *et al*., 2018). The largest part of energy expenditure (60-70%) is attributed to resting metabolic rate (RMR) and the biggest contributor of resting metabolic rate is the fat-free mass (FFM) made up by the brain, kidneys, gastrointestinal tract, liver and skeletal muscle; these contribute 75% of RMR. The fat mass (FM) contributing only 6.7% of REE (Figure 2) (Blundell et al., 2020). However, EE drives not only EI but energy storage as well; because energy supply has not been readily available through most of human evolution, a physiological mechanism of eating in excess of the immediate expenditure needs evolved; the excess energy is mobilized before the next meal becomes available. During next available meal, the depleted energy stores are replenished. Thus EE drives both EI and energy storage (Barboza & Hume, 2006). But what links energy expenditure to the brain mechanisms controlling energy intake? Hypothalamic AMP-activated protein kinase (AMPK) was proposed as the sensor of energy expenditure (Grannell *et al*., 2019). AMP is produced during energy expenditure through hydrolysis of ATP; the resulting increase in ADP: ATP and AMP: ATP ratio stimulates AMPK activity. Stimulation of AMPK activity with agouti-related protein and neuropeptide Y secreting neurons in the arcuate nucleus of the hypothalamus stimulates firing rate of these neurons and stimulates hunger and energy-intake; conversely, increased AMPK activity within proopiomelanocortin anorexigenic neurons of the hypothalamus decreased their firing rate. Ghrelin was found to activates whereas leptin, insulin, glucocagon-like peptide 1 (GLP-1) and its agonist liraglutide inactivate hypothalamic AMPK (Grannell *et al*., 2019).

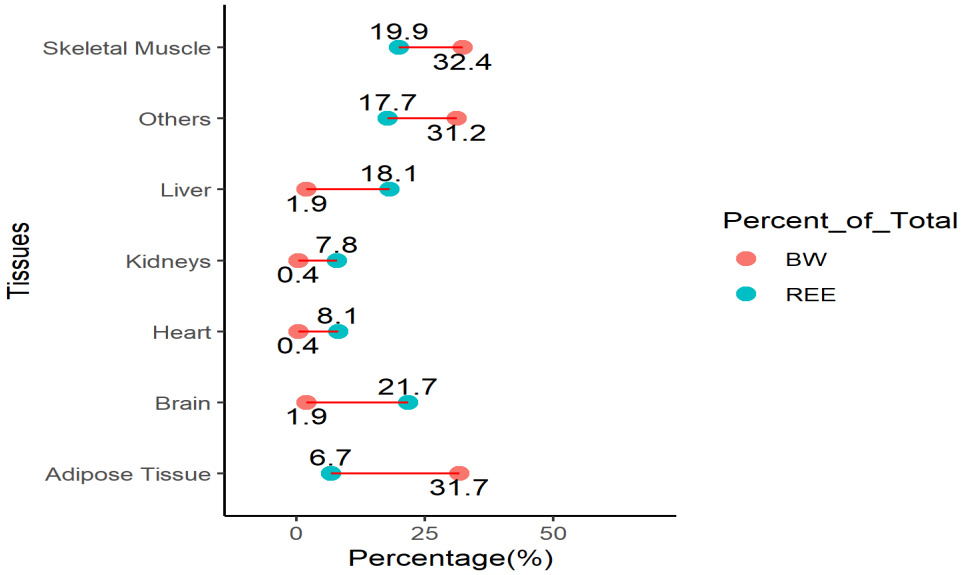


Figure 2: Contributions of Different Tissues to Body Weight (BW) and Resting Energy Expenditure (REE). Total Metabolic Rate = 1355.7 kcal/kg/day. Data Source: Blundell et al., (2018)

Obesogenic environment and leptin resistance

The obesogenic environment is characterized by availability of energy dense foods and reduced physical activity due to presence of mechanized work and transport (Speakman et al., 2011; Berthoud et al., 2020). Under positive energy balance, the obesogenic environment counters the leptin effects to reduce energy intake and increase physical activity. In such environments, increasingly higher but less effective levels of leptin are produced, a phenomenon known as leptin resistance (Beaulieu *et al*., 2018).

Physical activity energy expenditure (PAEE) represents one of the three components of total daily energy expenditure (TDEE) the other two being resting metabolic rate (RMR) and thermic effect of food (TEF). RMR, PAEE and TEF accounts for 60-70%, 15-35% and 5-15% of total daily energy expenditure (TDEE), respectively (Beaulieu *et al*., 2018). Figure 2.30 shows the relationship between physical activity levels and energy intake superimposed on body weight changes. The J-shaped nature of the intake against physical activity was first reported in the classical study by (Mayer *et*

al., 1956), replicated by (Shook *et al*., 2015) and confirmed by a recent systematic review (Beaulieu *et al*., 2016).

In regulated phase of Figure 3, leptin ensures stable body weight by matching expenditure to intake but in the non-regulated phase leptin resistance manifests where decreasing expenditure is associated with increasing energy intake.

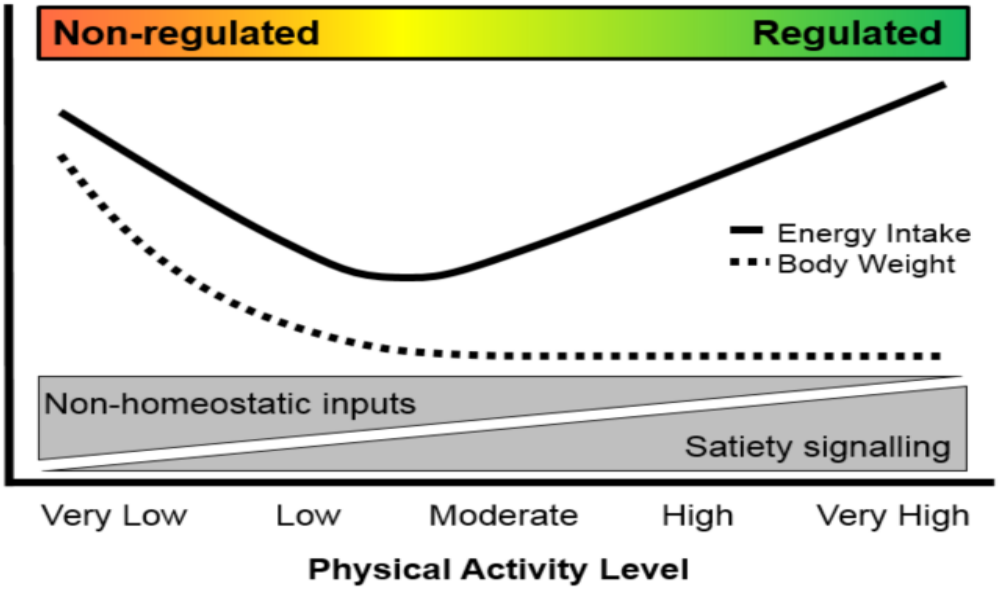
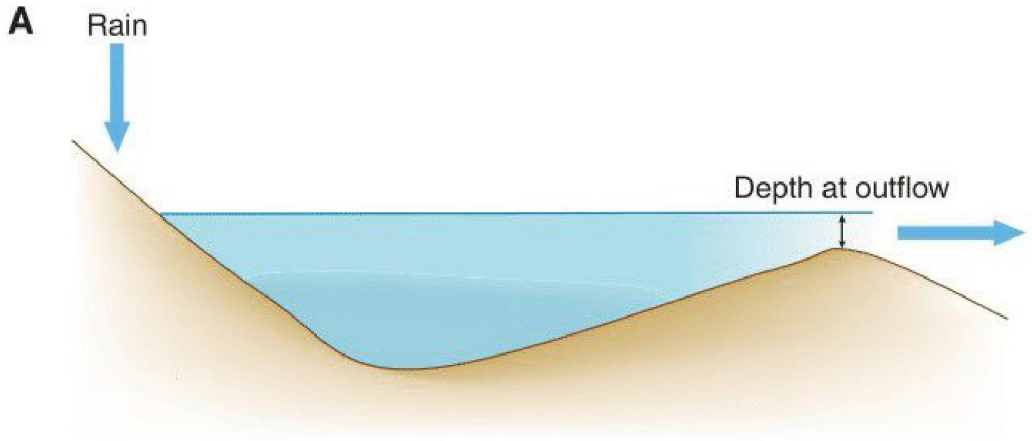


Figure 3: Relationship between Physical Activity Expenditure and Energy Intake. Source: Beaulieu et al., 2018

The settling point mechanism

Why the reduced physical activity of obesogenic environment does not cause reduced energy intake? Obesogenic environment does indeed reduce a component of total body energy expenditure i.e. physical activity related energy expenditure (PAEE). However, PAEE accounts for an average of 20% of total energy expenditure. Majority of the total body energy expenditure (65%) is formed by resting metabolic rate (RMR).

The obesogenic environment leads to higher fat mass and the latter mean higher energy expenditure to maintain the added fat mass. The higher expenditure stimulates higher EI (Blundell et al., 2020) which, in obesogenic environment, means higher fat mass and thus higher energy expenditure. A positive feedback mechanism is thus set with the end result being progressively increasing fat mass; this is the process that drives modern obesity epidemic. Thus energy expenditure and intake equalize to an ever changing point, hence the term settling point mechanism (Speakman et al., 2011). Figure 4 shows the analogy using water reservoir representing body fat stores and input to the reservoir (rain) representing the energy intake. The outflow represents energy expenditure. Panel A shows baseline and panels B and C showing matched changes in input and output to reflect new settling points.



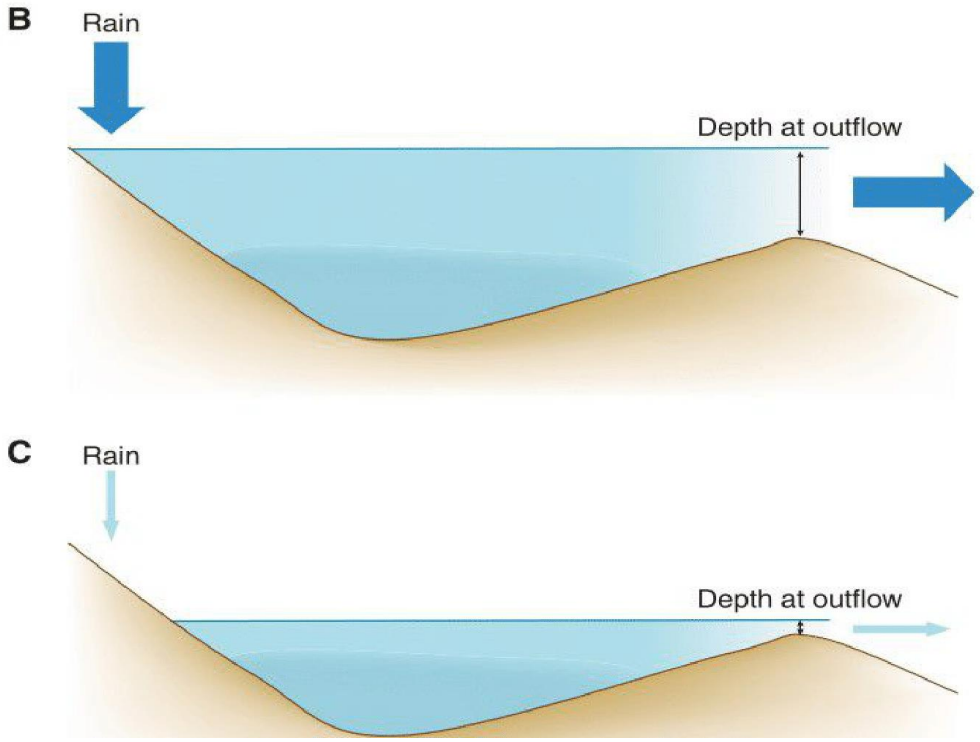


Figure 4: Settling-Point Mechanisms of Body Weight Regulation. Source: Speakman et al., (2011)

The modern obesity pandemic and the interaction between set-and settling point mechanisms

The increased intake in an obesogenic environment leads to accumulation of fat and increasing energy expenditure (settling point mechanism) and hence further increase in drive to eat (Blundell et al., 2020). On the other hand, any increase in fat mass will lead to leptin mediated inhibition of appetite; this inhibition is countered by increased expenditure-driven appetite (from the increased fat mass). Thus during periods of weight gain, settling and set point mechanisms work antagonistically (Figure 5B).

However, an attempt to reduce weight through reduced intake and increased physical activity will cause strong stimulation of appetite by both the settling and set point mechanism to match the increased physical activity related energy expenditure. Consequently, during situations of decreased fat mass, such as during weight-loss interventions, set- and settling point mechanisms work in harmony and augment each other; this explains the rapid regain of weight after any weight-loss intervention (Blundell et al., 2020) (Figure 5B).

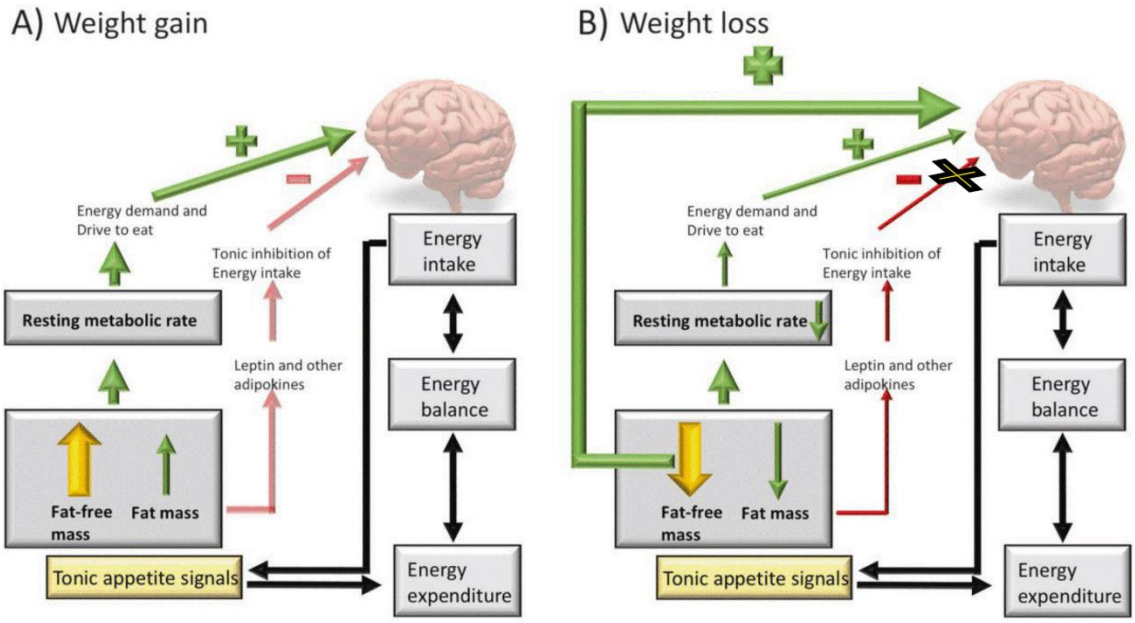


Figure 5: Relationship between Set- and Settling Point Mechanisms of Body Weight Regulation. Source: Stubbs et al., (2018)

Discussion

A relevant question to ask is what is the physiological significance of maintaining the fat mass at a particular set-point? Fat is known to be toxic to cells (lipotoxicity) and adipose tissue is known for its exceptional ability to store large amounts of fat without the effects of lipotoxicity (Stern *et al*., 2016; Rosen & Spiegelman, 2006).. Consequently, adipose tissue was known to serve as lipid 'sink.' Absence of fat, known as lipodystrophy, is known to be associated with ectopic fat accumulation and insulin resistance with diabetes. Excess fat also leads to 'overflow' from the adipose tissue 'sink' and ectopic fat accumulation, insulin resistance and diabetes. Thus excess and absence of fat are both dangerous as they lead to ectopic fat accumulation and impaired homeostasis (Stern *et al*., 2016; Rosen & Spiegelman, 2006).. During situations of increased fat mass (typical of modern obesogenic environment), set- and settling point mechanisms work antagonistically with the former promoting decreased energy intake and the latter promoting increased intake. Whether weight increases or not is determined by the balance between these mechanisms; the more obesogenic the environment the higher the tendency for progressively increasing fat mass, though under the constraint of lipostatic mechanisms. Obesogenic environmental factors such as fast-food retail exposure, urbanisation and urban sprawl are consistently linked with higher body weight (Lam et al., 2021; Ezenweke et al., 2022). Additionally, the set-point mechanism to prevent excess weight gain (leptin action) reaches a plateau at higher fat mass and leptin concentration (typical of all other enzymatic processes in the human body) such that leptin anorexigenic effects is attenuated in obese individuals. In other words, the higher the fat mass gain the lower the anorexigenic effects of leptin; on the other hand, there is no similar plateau for orexigenic effects of increased RMR from increased body mass; this further tilts the balance towards settling point mechanisms and weight gain (Stubbs et al., 2018 ; Blundell et al., 2020)

The striking feature of Figure 3 is that energy intake increases as one moves in both directions from low physical activity; both towards very high and towards very low physical activity levels. The increase in energy intake with increasing physical activity level is consistent with the conceptual formulations of settling point mechanisms earlier discussed. The fact that weight remains stable is a pointer to homeostatic mechanisms matching energy expenditure to energy intake. Interestingly, this 'regulated' phase of the curve is associated with lower body weight and thus higher leptin sensitivity. Conversely, the non-regulated phase of Figure 3 is also the phase of high body weight and impaired leptin sensitivity. A lower physical activity level means lower physical activity-related energy expenditure; however failure to match the intake to lowered physical activity level because of leptin resistance will lead to weight gain as excess energy is stored as fat. The increased fat mass will mean increased resting metabolic rate and increased energy expenditure (not shown in Figure 3) even though there is decreased physical activity-related expenditure; the result is increased intake from increased resting metabolic rate. Thus the increased energy intake in the regulated phase of the curve is due to increased physical activity-related expenditure; the increased intake in the non-regulated phase of the curve is due to increased resting metabolic rate expenditure from increased fat mass. The entire regions of the curve in Figure 2.30 is therefore consistent with settling- and set-point mechanisms earlier discussed.

CONCLUSION

While obesogenic environment counters leptin negative feedback mechanisms of reduced intake and increased energy expenditure, the same environment is consistent with the physiological process of settling point mechanism.

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