Mini Review

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Interpreting physiology to prevent pathologies associated with obesity and diabetes

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ABSTRACT

The approach by medicine and associated sciences dealing with the pathologies produced by obesity and Type 2 diabetes (T2D) has predominantly focused on the treatment rather than the prevention of the two health conditions. Both pharmacological and surgical approaches have been used in the treatment of both obesity and T2D. None is completely successful without incurring substantial side-effects including the option of permanent changes to the gastro-intestinal anatomy and physiology. This review puts forward for consideration two ideas: (1) That some of the failures in addressing prevention of obesity and T2D are the result of incorrect characterization of the neuroendocrine control of feeding and regulation of body weight, and (2) that there is a knowledge gap in how the capacity of the pancreas and adipose tissue, key organs in the pathologies of obesity and T2D, may be modified during two important periods of tissue proliferation, the second trimester of fetal development, the pre-pubertal growth spurt, and also possibly during recovery from substantial weight loss.

KEY WORDS: Insulin, leptin sensitivity, obesity, pathologies, resistance, weight regulation, type 2 diabetes

INTRODUCTION

Obesity and overweight conditions have risen rapidly in developed countries during the last half century. Currently, 34.9% of adult US population or about 78.6 million Americans are obese at an estimated annual medical cost of $147 billion in 2008 US dollars [1]. Obesity affects a significant number of pathologies: hypertension [2], atherosclerosis [3], hypercoagulability of blood [4], endothelial dysfunction [5] and associated increase in the risk of coronary vascular disease and accidents [6]. Excessive fat deposition in white adipose tissue (WAT) is accompanied by progressive decline in the sensitivity of WAT to insulin action [7,8]. When storage of additional calories in the WAT fails [8], pathological ectopic deposition of fat extends to the liver [9], pancreas [9], muscle [10], and kidney [11]. Excess fat deposition in these organs renders them also resistant to insulin action and results in excessive free fatty acid release from the WAT, increased hepatic glucose release, higher fasting glucose, and postprandial hyperglycemia [12]. Non-alcoholic fatty liver disease [13] and steatohepatitis [14] result from lipotoxic fat accumulation in the liver. Possibly the most damaging concomitant of obesity in developed countries is the progression from insulin resistance and pre-diabetes to Type-2 diabetes (T2D). The incidence of T2D has increased from 4.4 million or 2.4% of the US population in 1970s [15] to 29.1 million or 9.3% of the population in 2014 [16]. Hyperglycemia and compensatory hyperinsulinemia [17] associated with insulin resistance and glucose intolerance lead to pathological glycation of circulating proteins and formation of advanced glycation end products [18]. This progression ultimately leads to a pancreatic beta cells secretory failure [19] and apoptosis [20]. Insulin-resistant and diabetic muscle has reduced capacity to store glycogen [21] and take up glucose [22]. Insulin resistance and T2D lead to endothelial dysfunction [5] and microvascular pathologies including diabetic retinopathy [23], nephropathy [24], and neuropathy [25]. At the cellular level, the progression from insulin resistance to diabetes is accompanied by oxidative stress [26] and systemic inflammation [5]. Treatment of these obesity- and diabetes-associated pathologies has engaged medical practice, burdened the afflicted individuals psychologically [27] and physiologically [28], and imposed a $245 billion health care financial burden [29].

Medicine and associated sciences dealing with the pathologies produced by obesity and T2D have predominantly focused on the treatment rather than the prevention of the two health conditions. Both pharmacological [30-32] and surgical [33-34] approaches have been used in the treatment of both obesity and T2D. None is completely successful without incurring substantial side-effects [30,35,36], including the option of

permanent changes to the gastro-intestinal anatomy and physiology. This review puts forward for consideration two ideas: (1) that some of the failures in addressing prevention of obesity and T2D are the result of incorrect characterization of the neuroendocrine control of feeding and regulation of body weight, and (2) that there is a knowledge gap in how the capacity of the pancreas and adipose tissue, key organs in the pathologies of obesity and T2D, may be modified during two important periods of tissue proliferation, the second trimester of fetal development, the pre-pubertal growth spurt, and also possibly during recovery from substantial weight loss.

INCORRECT CHARACTERIZATION OF THE CONTROLS OF FEEDING AND THE REGULATION OF BODY WEIGHT

At least three widely-held hypotheses about the regulation of body weight may set back the development of improved preventive or corrective strategies. They are (1) the view that regulation of body weight is homeostatic or self-correcting by way of negative feedbacks which may convey a false confidence that this mechanism will guide the body mass to a healthy set point; (2) the position that body weight regulation is based on direct negative feedback from the WAT through secretion and actions of adipokine leptin such that leptin reduces adiposity by suppressing appetite and food intake and increasing thermogenesis; and (3) the concept that the regulation of body weight depends on the integrity of leptin actions in the brain and is inoperative in its absence. These three premises are not supported by experimental data. In discussing their inadequacies, the following three sections propose an alternative physiological explanation of the sequelae of obesity and a weight-regulatory schema that is supported by experimental data.

Body Weight Regulation is a Consequence of Non-homeostatic, Rather than Homeostatic, Feeding Controls and of Non-homeostatic Motivation for Physical Activity

Regulation of body weight stability entails defenses against its loss through compensatory adjustments in feeding, energy expenditure through thermogenesis and physical activity. A prerequisite for a homeostatic regulation of body weight would be the ability to sense calorie deficits generated by food restriction or energy expenditure of physical activity, and energy gain through calories eaten. There is ample evidence that within the context of daily meal-to-meal eating and episodes of physical activity, humans do not have the ability to track calories that are eaten, missing, or expended. Calories missing in the morning meal or expended during exercise are not made up during a subsequent meal [37]. The same volume of food is eaten when the opportunity for normal levels of activity is constrained [38], or when meals of different energy content are fed over an 11 weeks period [39]. The amount of food eaten is guided by food palatability [40,41], the opportunistic variables of quantity of food and drink offered [42,43], and social facilitation [44], but not the ability to track food calories [37]. The non-homeostatic nature of food intake leads to obesity as a result of exposure to "cafeteria diets" first demonstrated in rats given a variety of highly palatable and energy-dense foods in addition to their standard chow [45]. Eating is terminated by a sensation of fullness mediated by stretch receptors in the stomach wall [46,47] and relayed to the hindbrain nucleus of the tractus solitarius. The progressive rise in hunger during the inter-meal intervals reflects diminishing absorption of nutrients in the intestines. The intestines can sense nutrient quality [47] and affect the rate of gastric emptying and nutrient transit through secretion of several gut hormones [48].

Energy expenditure of physical activity contributes to the regulated weight plateau only if it is externally mandated. The weight of humans engaged in physically-demanding occupations is lower than those in more sedentary occupation [49]. Provided with a running wheel, rats engage in spontaneous running, and their weight stabilizes at a lower level than in caged animals not having this option [50]. Spontaneous physical activity, like feeding, also is structured non-homeostatically [51]. Despite contrary expectation, the motivation for physical activity increases with weight loss. Rats provided with a running wheel, and insufficient amount of food will increase their running in parallel with weight loss to the point of inanition [52]. Likewise, anorexic humans display a "drive to be active" [53]. By contrast, non-basal energy expenditure in humans declines in proportion to increases in adiposity [54,55] with almost complete inactivity in morbid obesity [56]. That this is an issue of the interaction between adiposity, and the motivation to move can be demonstrated by providing the negative external motivation. A foot shock at the base of a treadmill equalizes the duration and intensity or forced running in overweight and lean hamsters [57].

So how do non-homeostatic controls of feeding and physical activity achieve defended stability of body weight? They do so by having a functional connection within the framework of intermittent meal eating and movement. Episodes of intermittent opportunistic food intake lead to fullness and are associated with temporary suppression of motivation to move. Completion of meal processing reactivates the motivation to move and seek and initiate another meal. Depending on the amount of physical work required to obtain the resources for food, and on the quality, quantity and palatability of available food, the weight will stabilize at different regulated weight plateaus [49].

The insight that we are unable to track calories eaten or expended and are vulnerable to overeating palatable and abundant food while living in an environment largely devoid of the need for much physical work should guide individual decisions about how much to eat and move to maintain a healthy weight plateau. The additional insight that our motivation for physical activity depends on our adiposity should serve as a helpful cue to counteract non-homeostatic tendency to overeat and to engage in healthy levels of physical activity.

Meal-Associated Release of Gastric Leptin is the More Likely Contributor to Acute Energy Regulation than Adiposity-Associated Leptin Release from the WAT

The current and prevailing view of the weight-regulatory mechanism is that adipokine leptin secreted from the

subcutaneous WAT acts on the arcuate (ARC) and ventromedial hypothalamic (VMH) nuclei in a negative feedback fashion to influence brain circuits that inhibit feeding and increase energy expenditure [58-63]. This hypothesis, therefore, predicts reduced food intake and adiposity as fasting leptin concentrations rise in parallel with body fat level to inhibit feeding and reduce body fat. Fasting leptin [64] as well as insulin [65] concentration do rise in parallel with the increase in body fat [Figure 1]. This prompts a misinterpretation of a cause-and-effect relationship. This hypothesis is further strengthened by the observation of increased food intake that leads to obesity in animals [66] and humans [67] unable to secrete leptin, and by correction of both pathologies by administration of leptin [66,68]. This hypothesis has achieved the status of a dogma despite the following contradictory evidence. First, administration of a range of physiological and pharmacological doses of leptin to obese humans did not suppress their food intake or reduce their adiposity [69]. Second, high-fat diets [70] and cafeteria diets [45] easily induce obesity in animals and humans [71] despite the parallel increases in fasting leptin concentration and in adiposity. Moreover, third, and most damaging to the negative-feedback formulation of the hypothesis, leptin effectiveness in suppressing food intake and adiposity is inversely rather than proportionally related to body fat [72]. Finally in the daily episodic feeding circumstances, circulating concentrations of leptin change in response to the calories eaten or calories expended in exercise but bear no relationship to sensations of hunger, fullness, or the amount of subsequent food consumed [37].

An alternative hypothesis for the role of leptin in energy regulation is based on the evidence that in the context of intermittent meal eating, leptin is secreted by the chief cells in the gastric mucosa [73,74]. Postprandial leptin secretion and actions are yoked to meal-associated insulin secretion and actions in counter-regulatory fashion [75] [Figure 2]. The well-known postprandial insulin release that is sensitive to both calories ingested by mouth and calories infused intravenously [37] upregulates within 3-4 h the production and release of leptin [37,76]. Besides its exocrine release subsequent to its forming a complex with its soluble receptor to protect it from gastric acid, gastric leptin also reaches the systemic circulation. It does so

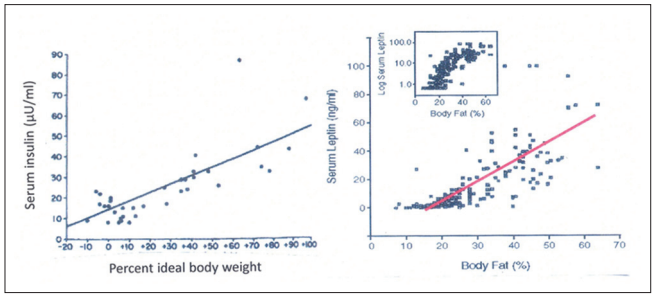

Figure 1: The proportional relationship between body adiposity and fasting concentrations of fasting serum insulin (left) and fasting serum leptin. The relationship reflects progressive loss of tissue sensitivity to the two hormones that changes in parallel with the loss of receprors of the two hormones on the target cells. Data for insulin from reference 65 and for leptin from reference 64

by being transported to the duodenum where it binds with its receptor on the luminal membrane from where it is transcytozed to the Golgi apparatus of the duodenal enterocyte. There it again binds with its receptor and leaves intestinal mucosa for systemic circulation [77]. In opposition to the anabolic and parasympathetic actions of insulin to facilitate cellular uptake and storage of nutrients and to suppress mobilization and utilization of these nutrients, leptin counter regulates insulin actions by blocking its release [78] and blocking insulin binding to its receptors [79]. Leptin also increases lipolysis and lipid utilization [80,81] by mobilizing lipids stored in the adipose tissue [81], liver [82], and the muscle [83,84]. It therefore contributes to meal-to-meal balancing of positive energy balance caused by food intake, in contrast to hormones such as catecholamines, glucagon, cortisol, and growth hormone that are recruited for production of emergency fuels in response to negative energy balance. In addition to diurnal leptin secretion in response to the postprandial insulin stimulus, leptin also exhibits a circadian pattern of secretion [85] that is also sensitive to energy balance. The acrophase of circadian leptin rhythm is in the middle of the night [85] and increases after excess diurnal energy intake and declines after diurnal energy deficit [86].

The counter-regulatory relationship of leptin and postprandial insulin helps explain the paradoxical relationship of leptin to body fat as postulated by the homeostatic concept of weight regulation. The fasting concentrations of the two hormones change in lockstep with increases in body fat mass [Figure 1]. The increases in the fasting concentrations of both insulin and leptin reflect increases in tissue resistance to their actions. This is a consequence of the fundamental endocrine principle that the sensitivity of peripheral tissues to fasting concentration of a hormone declines in parallel with the number of hormone receptors on the target cell surface [Figure 3] [87] and with the degree of repletion of target tissues with storage fuels. As the amount of lipids and glycogen in the WAT [88], muscle [89,90], and liver [91] increases, the number of insulin receptors on their cell surfaces declines. At equal Km, tissue sensitivity to hormone increases in proportion to the number of "spare receptors" above the number required to elicit a biological response [Figure 3a] [87]. With a smaller number of receptors in energy-replete cells, resistance to a hormone manifests in the form of a higher hormone concentration required to elicit the biological response [Figure 3b].

The parallel rise in the fasting concentrations of insulin and leptin represents the cellular mechanism contributing to the regulation of body weight. Through increased sensitivity to insulin, triglyceride-depleted adipocytes, and lipid- and glycogen-depleted liver and skeletal muscle, are more responsive to insulin actions leading to heightened nutrient uptake and storage. Moreover, the counter-regulation of insulin by leptin controls the amount of fat storage in tissues and thus contributes to the maintenance of insulin sensitivity [80,92]. The pathologies observed in obesity and T2D simply reflect the operation of insulin and leptin above their physiological range. There is a need for systematic study of dietary and exercise conditions that reduce postprandial insulin and enhance postprandial leptin action. Such data could then inform and

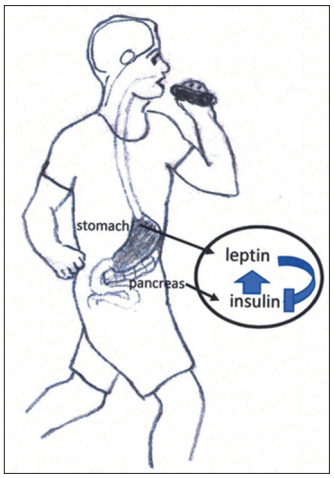

Figure 2: The counter regulatory relationship between postprandial pancreatic insulin secretion and action and postprandial gastric leptin secretion and action. Insulin secretion associated with meal eating upregulates production and secretion of gastric leptin. Gastric leptin inhibits insulin secretion, its binding to insulin receptors, and counteracts insulin's anabolic actions

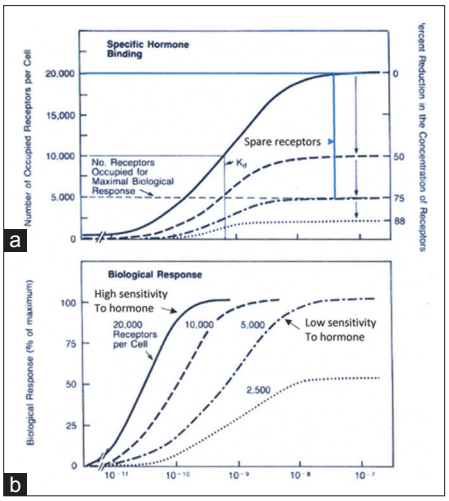

Figure 3: The sensitivity of peripheral tissues to fasting concentration of a hormone declines in parallel with the number of receptors on the target cell surface and the degree of repletion of target tissues with storage fuels. As the amount of the storage fuel in the target cell increases, the number of insulin receptors on the cell surfaces declines. At equal km, tissue sensitivity to a hormone increases in proportion to the number of "spare receptors" above the number required to elicit a biological response (a). With smaller number of receptors in energy replete cells, resistance to a hormone manifests in the form of a higher hormone concentration needed to elicit the biological response (b). From reference 87, with permission of the Oxford University Press

guide adjustments in feeding and activity behaviors to better match energy intake and expenditure for the maintenance of healthy body weight level.

Weight Regulation Depends on the Interaction of the Sympathetic and Parasympathetic Components of the Autonomic Nervous System and Not on the Integrity of Leptin Signaling

Several decades ago, the autonomic component of the central nervous system (ANS) was recognized as the principal regulatory agent for balancing energy intake and expenditure [93]. Lesions of the ARC and VMH nuclei appeared to shift the balance between the sympathetic energy expending ANS division in favor of the parasympathetic ANS division responsible for over secretion of insulin and obesity [93,94] both of which were preventable by transection of the parasympathetic nerve vagus [94]. Since then, additional evidence accumulated that ANS also controls circadian and ultradian periodicities of meal taking, food processing, and controls thermogenesis and spontaneous physical activity [75,95]. Since the discovery the capacity of leptin to suppress feeding and adiposity in animals [66] and humans [68] unable to produce leptin, the research and interpretive focus has shifted from the regulatory role of ANS to the analysis of leptin actions on the hypothalamic and midbrain circuits regulating feeding and thermogenesis [96] with the implicit hypothesis that the integrity of the leptin signaling in the brain is the essential prerequisite for the regulation of body weight. The assumption that weight regulation does not operate in the absence of functional leptin-brain interactions is not supported by facts. Animals with the lesions of the ARC-VMH hypothalamic targets of leptin action continue to defend their elevated weight and fat plateau against losses [97]. Furthermore, if animals are rendered obese prior to the damage of the VMH-ARC targets of leptin action, they do not overeat or over secrete insulin. Instead, they maintain their elevated fat plateau without hyperphagia or insulin over secretion [98] suggesting that removal of leptin action in the brain increases the level at which the body fat is maintained but does not abolish the defense mechanism against body weight loss. So while destruction of some brain targets of leptin action increases adiposity, it does not remove the role of the ANS in regulating the higher weight and fat setpoint.

The early interpretation of actions of leptin in the brain as a direct and proportional regulator of adiposity through adjustments of feeding and thermogenesis is slowly giving way to the recognition that within their physiologic concentrations, leptin and insulin suppress the reward value or salience of food [40,41] as well as the motivation to be physically active [99,100]. A decline in their concentrations increases the strength of these motivations. Whether the brain substrates over which leptin and insulin exert these suppressive effects are confined to nucleus accumbens in the ventral striatum [40,41] or also include some hypothalamic nuclei [101] remains to be worked out. This reinterpretation of the actions of insulin and leptin in the brain dovetails with the non-homeostatic control of feeding and physical activity in weight regulation. By virtue of the changes in hormone sensitivity as a function of adiposity [Figure 1], the withdrawal of insulin and leptin in underweight state facilitates feeding and physical work to procure food as well increases the efficiency of energy storage when the metabolic fuel stores are depleted and peripheral and brain sensitivity to the two hormones is maximal. As the compensatory eating and enhanced efficiency of food storage restore the WAT lipid stores and muscle lipid and glycogen stores, rising tissue

resistance to insulin and leptin actions and the suppression by higher concentrations of the two hormones of the motivational brain substrates stabilizes body weight at the pre-deprivation level. The ultimate understanding of the weight regulatory mechanism will require a shift from the current preoccupation with leptin action on hypothalamic circuits to the analysis of the role of ANS in balancing parasympathetic and sympathetic controls over secretion insulin and leptin and their actions on metabolism.

HOW TO INFLUENCE THE PHYSIOLOGY IN ORDER TO PREVENT THE PATHOLOGY

The obvious solutions to avoiding the pathologies that result from overeating and obesity and that lead to T2D would require implementation of social policies to reduce easy availability of highly palatable foods and to impose requirements for greater physical work. Obviously, such utopian plans will not be feasible in open-market democratic societies. That it can be achieved in the context of a totalitarian society experiencing food shortages is illustrated by the example of Cuba, where food intakes, body weights, and pathologies associated with obesity and T2D were minimized through reduced access to food and increased physical work requirements [102].

An alternative to pharmacological and surgical treatments of obesity - and T2D-associated pathologies would be to close the knowledge gap on how body fatness and pancreatic beta cell capacities could be influenced during developmental growth. The most damaging pathologies of obesity in adulthood are the result of exceeding the capacity of the adipose tissue for fat storage which leads to ectopic fat accumulation and lipotoxicity in the liver, pancreas and other tissues [103]. The most damaging pathologies of adult T2D are the consequence of hyperglycemia and compensatory hyper-insulinemia leading to progressive apoptosis of pancreatic beta cells. There is a lack of knowledge whether modifications of nutrition and exercise could epigenetically modify the proliferative capacity of pancreatic beta cells and WAT adipocytes to resist the damage inflicted by overeating and excessive storage of nutrient energy. The likely windows of opportunity for epigenetic modification of these two tissues include the periods of rapid cellular proliferation during the second trimester of intrauterine growth and during the pre-pubertal growth spurt [104]. It is not clear why the negative energy balance during pregnancy generated by dietary restriction and exercise produces opposite effects. Dietary restriction during later stages of pregnancy reduces overall fetal growth and organ size [105-109]. Offspring subjected to intrauterine growth retardation have reduced pancreatic β cell mass [105-108], increased fasting insulin, reduced glucose tolerance [108], and increased hepatic insulin resistance [109]. On the other hand, exercise energy expenditure during pregnancy which also reduces overall offspring growth and body fat measured at birth [110,111], at 1-year of age [110] and at 5 years of age [111] affects glucose tolerance and insulin sensitivity in the opposite way. Infants of exercising mothers weight about 6-7% less than of non-exercising pregnant women, are about 7% shorter, and have 25-31% less body fat [110,111]. At age 5, their subcutaneous skinfold measurements are 16% lower than those in offspring of sedentary mothers [111]. If forced to swim, weanling rats (which are born in less mature state than human infants), display reduced adipocyte cellularity [112]. Yet despite reduced body and individual organ size at birth as a result of maternal exercise during pregnancy, such rodents in adulthood display improved glucose tolerance [113-115], and systemic insulin sensitivity measured by hyperinsulinemic hyperglycemic clamp [114]. Why energy restriction during pregnancy by dietary and exercise means produce opposite results is not known. Nor is it known why children of obese mothers, as well as children of mothers experiencing dietary restriction during pregnancy, experience increased risk of insulin resistance and T2D [116]. Clearly, this is an area in need of systematic research to increase the understanding how exercise and diets may affect pancreatic and WAT development.

Another window of opportunity for potential epigenetic changes in body composition and pancreatic beta cell capacity may be the period during maintenance of, and recovery from, diet-induced weight loss. Rats exposed to exercise during weight-loss maintenance display reduced rate of weight regain during ad libitum re-alimentation [117]. Leptin treatment during weight-loss maintenance in humans reduces hunger and increases thermogenesis [118]. Leptin treatment during weight loss maintenance reduced body fat regain in non-growing hamsters and repartitioned body composition in favor of lean body mass in growing hamsters [119]. That leptin could produce epigenetic changes in the brain targets of its action is seen in functional enhancement of the activity of brain areas involved in detecting the salience and rewarding value of food during fasting in three hypoleptinemic subjects treated with leptin [120]. The knowledge gap regarding whether manipulations reducing WAT cellularity are beneficial or increase insulin resistance as is the case in lipodystrophy also needs to be closed.

The ideas proposed in this review are intended to encourage a research focus toward (1) a better understanding of the mechanism of human feeding and locomotion to empower individuals with information on how to prevent overeating and excessive weight gain; (2) an understanding of the counter regulatory relationship between insulin and leptin in the context of meal-to-meal eating to produce data that could define optimal relationship between calories eaten and expended; and (3) closing the information gap regarding the influence of quantities and qualities of nutrients and quantity and type of exercise during growth periods and recovery from weight loss when the cellularity of adipose and pancreatic endocrine tissues may be sensitive to epigenetic modification. This type of research would augment the understanding of physiology and reduce the burden of the pathological consequences of obesity and T2D.

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