You are what you ate: The Biosetpoint Hypothesis

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Summary  The current epidemic of obesity has developed at a rate that cannot be attributed to genetic drift. Attempts to treat obesity using diet and activity have been largely disappointing. Genes are fixed at conception, but genetic expression is known to be influenced by nutriture during the stages of growth and development, these occurring in humans from conception through arrival at adulthood. Based on an extrapolation from existing data and cultural models, it is hypothesized that there is a mechanism by which diet and lifestyle habits present during the individual stages of growth and development help to define and program genetic expression in a way that resists change. It is through this mechanism that current nutritional and lifestyle practices have impacted genetic expression and contributed to the rapid development of resistant obesity. The details of the interaction between nutrition, lifestyle and genetic expression during growth must be examined, and intervention strategies devised for early stages of growth to prevent the seeds of obesity from taking root.

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Introduction

Public health statistics continue to describe the obesity juggernaut changing the landscape of human morphology [1–7]. Aggressive surgical and pharmaceutical interventions are utilized for serious cases, but most solutions are linked to the underlying belief that causation as well as amelioration rests with changes in diet, lifestyle and other volitional behaviors [8]. Achieving and maintaining weight loss, however, remains problematic [9,10], providing an open door for radical diets and questionable nostrums all marketed as a quick-fix for this stubborn health dilemma [11]. It is known that an individual’s genotype is determined at conception and is unalterable. The phenotype, a physical manifestation of the way the genes express themselves, is a product of the interaction between the genetic instructions and the various environmental factors present during development. There is no evidence that genetic changes are responsible for the current epidemic of obesity. For clues to the ontogeny of obesity we will need to identify any patterns or mechanisms that may have contributed to the increased frequency of the obese phenotype, and its resistance to treatment.

Hypothesis

The cellular environment present during periods of rapid cellular growth and development (flex periods) helps determine phenotypic expression. At the termination of the flex period, the existing phenotype will be fixed as a ‘‘Biosetpoint,’’ and it is then...
defended by the organism during the ensuing non-growth interval. An existing Biosetpoint is subject to further refinement during subsequent flex periods, the range of potential modifications reflecting the genetically determined stages of growth and proceeding until adult status is achieved.

The model of an orderly creation and defense of Biosetpoints, coupled with the unique vulnerability to dietary and lifestyle effects during the flex periods, helps to explain the rapid explosion of obesity in our population. Further, this mechanism provides a rationale for the resistance of the obese phenotype to intervention. An investigation of the Biosetpoint hypothesis may lead to important advances in our understanding of the etiology and treatment of obesity as well as other conditions vulnerable to the biochemical conditions during growth and development.

Evaluation of the Biosetpoint hypothesis

Phenotypic pliancy

There are data to suggest that the phenotype is particularly susceptible to the nutritional environment during periods of cellular growth and development. For example, neural tube defects are associated with inadequate folic acid during specific phases of fetal development [12]. Iron deficiencies during childhood impact cognitive and motor development and behavior [13]. The presence of adequate levels of docosahexaenoic acid (DHA), an N-3 long-chain polyunsaturated fatty acid, has been shown to play an important role in many aspects of brain development, including an association with adult intelligence; this nutrient is now being used to fortify infant formula [14,15]. It is important to note that deficiencies of these nutrients at other times during the life cycle do not have similar effects.

Other types of nutritional modifications during pregnancy and lactation, including overfeeding or seeming benign dietary adjustments, can also have persistent effects on the neonate [16–18]. This type of evidence contributes to our understanding of the interaction between nutrition and development, but more importantly it supports the concept that the phenotype is particularly responsive to environmental factors present during periods of rapid growth and development. In humans, such periods occur in utero, during infancy, childhood, adolescence, young adulthood, as well as during pregnancy and lactation.

An additional example of growth and development is the interval following a period of caloric deprivation that is sufficient to give rise to a period of compensatory growth. Several animal studies suggest that caloric restriction (undernutrition without malnutrition) alters gene expression and enhances disease resistance, longevity, and age-related functional decline [19–23]. Cell proliferation in C57BL/6J mice was significantly reduced by a 33% calorie restricted diet, or one in which a 95% of an ad libitum diet was provided on an intermittent basis, only three times per week [24].

It is reasonable to project, therefore, that the nutritional environment associated with a period of growth and development will have an ability to impact the genetic expression resulting from that stage of development. The “Biosetpoint,” which is the genetic-expression product of each stage of developmental, is then defended by the body during the homeostasis that follows. Each Biosetpoint remains in effect, serving as the template for genetic expression until the next stage of growth and development during which more of the adult phenotype would be determined.

If an aspect of development takes place during one specific stage of growth, the nutritional environment associated with that period would be critical. An example of this would be the role of folate during neural tube development in the early weeks of fetal life.

Viewing the course of development in this manner lends more clarity to the rapid explosion in the incidence of obesity as well as its resistance to intervention. Not only does this approach view the process of arriving at adulthood as a sequence of developmental steps, it encourages a focus on the nutritional environments associated with specific periods of actual growth and development.

If the presence of the obesity epidemic correlates with widespread changes in nutrient intake during critical developmental periods, such changes should be investigated as potential causal or contributing factors toward the increased presence of the obese adult phenotype.

Evidence from nutrition correlates to the obesity epidemic

With the human diet it becomes difficult to assign causal or contributing roles to specific food components as they may only be indicators of general dietary imbalance which itself influences long-term health. Data from the HANES-I national survey found that neither caloric intake, nor caloric intake adjusted for physical activity and age was higher in obese subjects [25]. It was also observed that food selection by the obese tends to be of poor nutrient value [26].
In recent decades, intakes of two food components, simple sugars and trans fats, have been elevated during the growth periods of childhood and adolescence [27,28]. Several studies have demonstrated that the consumption of sugar-sweetened drinks correlates with the obesity epidemic [29–31] and the risk of type 2 diabetes [32]. A 15-year prospective study of fast-food habits shows a direct association between intakes of these drinks and insulin resistance [33]. Trans fats freely cross the placenta and are found in the developing fetus in similar concentrations as in the mother [34]. There is an inverse relationship between maternal trans fat levels and the length of gestation, birth weight and length of the neonate [35]. Trans fats appear in maternal milk in correlation with the level in the maternal diet and have been associated with increased insulin resistance in the child, this in turn being associated with a higher risk of obesity, diabetes and metabolic syndrome in later life [36]. During lactation, the level of trans fats in human milk is inversely related to its level of essential fatty acids, and the levels of trans fats and essential fatty acids in the milk correlate with those found in the plasma triglycerides and phospholipids of the breast-fed infant [37]. The major dietary sources of the trans fats were bakery products, snack and fast foods. Foods containing trans fats now figure prominently during the developmental periods of gestation, infancy, childhood and adolescence, in many cases being offered on a regular basis through foods provided at school, and through fast food outlets and vending machines [38].

Intakes of vegetables and fruits during key developmental stages are low [39]. In addition, there are suggestions that the existing lower intakes of certain food components and essential nutrients during development are having specific effects on genetic expression that are associated with the increased risk of obesity [40].

Cross-cultural evidence

The Biosetpoint theory posits that the adult phenotype represents the cumulative effects of the nutritional environments during development. That being the case, individuals who are raised in a different food culture should have risks of obesity at variance from those born and raised in the US. Additional support for the concept of the Biosetpoint, therefore, could come from examining cross-cultural models. Preliminary support for this logic is supported by data that foreign-born adolescents who immigrate to the United States have a lower risk of obesity than adolescents born here [41], as well as data that the age-adjusted risk of obesity among most immigrants groups does not approach that of US-born unless the duration of residence has been at least 15 years [42].

Implications of the Biosetpoint hypothesis

The Biosetpoint hypothesis can help explain differential effects from treatments administered during a growth period, versus ones administered at other times. As such it would represent a new variable to be considered in data evaluation and experimental design. One dietary example, conjugated linoleic acid (CLA) is illustrative of this phenomenon. CLA refers to a group of conjugated dienoic fatty acid derivatives that occur naturally in dairy products. CLA is being sold as a dietary supplement primarily because research on experimental animals and isolated cells demonstrated an ability to decrease percent body fat and increase lean body mass with some effects persisting beyond the treatment period [43,44]. Data on humans, however, including a metabolic ward study have not been encouraging [45,46]. Of interest is the fact that animal studies typically administer the CLA during the post-weaning period, where there is rapid growth and development, whereas most human studies have used adults at homeostasis. When the CLA was given to humans following three weeks on a calorie-restricted diet, the treatment revealed a dose dependent decrease in %body fat, and increases in fat-free mass and resting metabolic rate [47]. The different results from the CLA may have been due to its administration during a period of post-deprivation compensatory growth.

Discussion

If the roots of the obesity epidemic are not intertwined in genetic drift, suspicion then falls upon environmental factors that affect genetic expression. The usual suspects in the environment are an excessive intake of food coupled with decreased levels of physical activity [48]. If too much food and too little activity are indeed the cause, at issue is the difficulty encountered when attempting to achieve and maintain weight loss through diet and exercise, or through any method short of pharmaceutical or surgical intervention [49].

A sequence of programmatic steps during which genetic expression is formulated, fixed and subsequently defended lends metabolic credence to the rapid onset of the obesity epidemic, and it also helps explain the riddle of resistance. This type of developmental mechanism could provide clues to
the etiology and pathogenesis of other phenomena, such as obesity-related variances in regional body composition, changes in body morphology following pregnancy, and the effects and sequelae of caloric deprivation and fasting. The long-term impact of early nutrition has been previously considered [50–52], but the approaches have tended to be observational, failing to consider the individual stages of growth and development as a sequence of programmatic steps and refinements.

One of the limitations of the Biosetpoint hypothesis is its reliance on factors present during specific periods of growth and development. Animal models can be useful. For example, animal data support the notion that perinatal overnutrition and under-nutrition help determine the adult appetite regulatory system [53]. Animal studies have also revealed the presence of a compensatory recovery of body fat after adipose tissue has been surgically removed [54]. Human growth, however, is multi-phasic and not on a set timetable in the latter stages. Data can be gathered from early stages where rapid growth is predictable. There is, for example, epidemiological data suggest that weight gain during the first week of life is associated with the risk of overweight in adulthood [55]. However, to facilitate study of this mechanism throughout the growth cycle there will need to be an identification of biological markers for the onset and termination of the various developmental periods. Clinical studies could be then be designed to gather data on existing behaviors and interventions at various points during the growth cycle to assess their impact on the development of obesity, its various subtypes or its markers. Additional epidemiological support for the Biosetpoint hypothesis could be gathered from population studies that record inter-cultural migrations; analyzing the age at which the migration occurred and the association with the risk of obesity.

Conclusion

Obesity has been characterized as a chronic, relapsing neurochemical disease [56]. There has been limited success intervening and reversing obesity using the current acute care model. Extrapolation from existing data suggests the existence of a mechanism by which the interaction between environmental factors and genetic instructions contributes to the formation of a developmental Biosetpoint that is, in effect, a byproduct of each stage of growth and development. This Biosetpoint is then adhered to during the subsequent homeostasis. Such a mechanism provides a rationale for the status quo with its stance that classical treatments of resistant pathologies, such as obesity, may be specifically opposed by endogenous programming. With this understanding, we can develop more efficient intervention strategies for our youth and more effective treatments for those already suffering from this condition. At present, there are cautions against the use of medications during pregnancy and lactation. These concerns, if not based on hard data, stem from the principle it is essential to be able to affirm safety for use during these important developmental periods. There is, however, a lack of special consideration toward diet and nutrition during other key developmental periods of life. Factors present during periods of rapid growth and development may be helping to define and fix genetic expression. The unknown footprints of such factors may have already orchestrated wholesale changes in human health and morphology. There is a logical interest in the successful treatment for obesity. However, much will be gained by more study on the mechanistic roots of this condition.

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References


