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Metabolic Diseases: the Environment Determines the Odds, Even for Genes

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The odds for well-being or illness are determined by the interplay of genetic and environmental impacts. In this review, normal and disturbed body weight regulation are used to demonstrate the role of integrative bioresearch in bridging the gap between identified genotypes and an understanding of the functions of redundant and plastic control systems underlying phenotypes.

Evolution is characterized by increasing plasticity and redundancy of control systems rather than by an increasing number of genes. The crucial impact of the environment on the development of phenotypes has been known as long as the laws of genetic inheritance. However, in the wake of the enthusiasm generated by unraveling the human genome, the distance between this milestone and understanding the (patho)physiology of multigenically determined complex traits has been underestimated. Focussing on the “blueprint of life,” the genome, may be adequate in the functional analysis of cell conglomerates communicating via ligands and receptors, but it is insufficient to elucidate the fundamental differences in function between human, mouse, and fly. The recent conclusion that the number of genes has only moderately increased during evolution strikingly contrasts with the exponential gain in plasticity and redundancy of the nervous and humoral systems controlling autonomic and behavioral responses. In fact, the degrees of freedom offered by plasticity and redundancy are crucial organizational advantages of higher organisms. Moreover, they provide the lever for extensive environmental modulations of the genetic program, particularly during the early stages of ontogeny. In higher organisms, these influences are not only transmitted by the chemical and physical properties of the environment acting on the organism’s surface but are also perceived by sensory organs that transmit their information via neural and hormonal messages to the brain. The resulting complexity is further increased by this information transfer being filtered by gateways under the control of signals emitted from the brain.

Obesity epidemic: the impact of rapid environmental changes on genes selected over millions of years

Understanding how physiological translation of the genome is environmentally modulated is particularly relevant for human health problems like obesity, which involve altered controls at all levels of integration from tissue metabolism to behavior. As a major health risk in industrialized societies (known to multiply the risks for hypertension and associated heart problems, diabetes, and orthopedic diseases), obesity, once established, can be temporarily mitigated but not permanently cured at present (6, 8). In attempts to elucidate its pathogenesis, genetic predispositions have received great attention, although the underlying cause of the dramatic increase in obesity prevalence in industrialized societies within the last few decades is most likely the change in environmental impacts. Accordingly, a genetic program having evolved over millions of years to optimize redundant physiological systems dealing with food shortages and with high energy costs is faced today with the opposite challenge. That is, these systems now have to maintain constancy of energy stores in conditions of excessive food continuously available at little energy cost. The hypothesis that “thrifty genes,” selected during periods of food scarcity, underlie the high prevalence of obesity and type 2 (non-insulin-dependent) diabetes in some ethnic groups (e.g., the Pima) was originally put forward by J. V. Neel. This idea was further supported when E. Ravussin found that this phenotype occurs in the Pima population living in the United States but not in Pima subgroups in very poor, rural areas of Mexico.

Combining structural with systemic analysis to identify causes of obesity

Even in monogenic forms of obesity, identification of the molecular defect poses rather than answers the question. Efforts to elucidate the multigenic basis that is thought to underlie most cases of human obesity have just begun, but molecular identification of monogenic defects causing failures of body weight (fat mass) regulation in animal models have distinctly advanced our understanding of these regulatory systems. In the ob/ob mouse, the absence of leptin, a hormone newly identified in 1994, was recognized as the cause of this form of obesity (Zhang et al., cited in Ref. 1). Within two years, the receptor for this hormone was identified, and mutations in its gene were found to be the causes of other forms of extreme obesity, long known from animal models such as the db/db mouse and the fa/fa Zucker rat (see references in Ref. 1). At the molecular level, the fa mutation of the leptin receptor encodes the exchange of just one nucleotide for another, altering one amino acid at a critical site in the receptor (Fig. 1). However, this mutation does not tell us how its homozygous presence causes the adult rat to have twice the normal body mass, more than twice the normal body fat, and abnormalities in hormonal and neuronal control systems, ranging from food intake to reproduction. Understanding how these changes develop...
requires detailed analysis of the entire feedback loop responsible for normal or pathological body weight regulation and its interaction with other control loops. Attempts to separate primary (causative) from secondary (aggravating) factors in the adult, obese animal appear nearly hopeless. Better chances, however, are offered by analyzing the ontogeny of this disturbance to understand the primordial, pathologically altered, and normal functions of leptin and its receptor.

Clarifying the consequences of the fa mutation as an example of clarifying the functional genomics of energy balance control. Physically, there is only one possible cause of obesity without drastic reduction of lean body mass: the organism must have absorbed more metabolizable energy than it has expended. Even in the fa/fa Zucker rat, which is frequently considered a case demonstrating the deposition of extra fat at the cost of lean body mass, <5% of the extra fat mass found in adult animals can be calorically accounted for by reduced lean body mass, considering that 1 g of fat mass is energetically equivalent to 2 g of fat-free dry mass. Thus the fa/fa obesity, like most forms of obesity, is ultimately due to caloric imbalance.

To understand why the fa/fa genotype results in obesity, the consequences of the defective leptin receptor need to be tracked from the cellular level, via the nervous-humoral system, to the energy balance level. The functions of the intact, signaling, long-form receptor subtype (1, 7) within the central nervous system are summarized in Fig. 2, left, and illustrate the multitude of potential disturbances caused by the defective receptor. The chain of events from receptor responses to energy balance changes can be additionally modified by environmental impacts at each level (Fig. 2, right). At the energy balance level, food availability and food composition as well as ambient temperature will decisively alter the effects of leptin and the resulting adiposity phenotype (see references in Refs. 3 and 13). Influences of sensory stimulation by attractive food (via cephalic-phase insulin secretion) or changes in response to stress (via alterations in the hypothalamic-pituitary axis) are examples of environmental modifications via nervous-humoral modulation (10). Neuronal circuits may change with use (e.g., as the consequence of preceding nutritional experience), and thereby the environment may alter leptin receptor function even at the cellular level (9).

The relation between the genetic defect and the resulting phenotype becomes even more complicated when considering that the defect will also affect leptin receptor populations outside the central nervous system. For example, deficiency of the signaling, long form of the receptor on fat cells may disturb cellular metabolic adjustments to environmental changes, such as altered compositions of absorbed nutrients. To add to the complexity, the fa lesion also affects the short forms of the leptin receptor (1, 7), like the one that is assumed to function as a carrier (transporting leptin across the blood-brain barrier) and seems to be upregulated in response to high-caloric food (discussed in Ref. 7).

The example of the leptin receptor-deficient Zucker rat makes it obvious that sophisticated molecular and cellular techniques have to be combined with equally sophisticated systemic approaches to achieve the analytic potency required for unraveling the functions of such control systems. Moreover, it has to be considered that altered physiological responses not only occur as immediate consequences of the genetic defect but might be the final result of a long chain of indirect, and partially counterregulatory, responses to the primary lesion, as has been recently documented for the abnormal regulation of leptin expression in this animal model (17). Thus adequate analysis is only possible if the new tools and research directions provided by molecular genetics are incorporated into long-standing integrative experimental approaches suited to clarify the functioning of a system characterized by enormous plasticity and redundancy (1, 7, 8, 13, 17). Considering the complexity of analyzing monogenic forms of obesity, it becomes obvious that unraveling the physiological alterations (and possible causal therapeutic measures) in even a single individual case of the typical, multigene-dependent human obesity (3, 8) would require functional analysis of numerous mutated genes, including their interactions with each other as well as with the environmental impacts individually experienced during pre- and postnatal life.
Gene-environment interactions

Different susceptibility for gene-environment interactions. Phenotypic penetration of genetic alterations will often be strongly dependent on environmental impacts, thus complicating attempts to draw a simple line from a gene to a function in a complex control system. However, susceptibility to environmental impacts differs among genotypes, with fa/fa or ob/ob representing cases in which the obesity phenotypes are not much affected by environmental modifications. In the fa/fa genotype, the presence of two mutated alleles for the leptin receptor (Lepr<sup>fa</sup>) inevitably results in a massively obese phenotype, and if food supply is limited throughout life to that of wild-type (+/+) animals, extra fat is deposited even at the cost of lean body mass. Nevertheless, the phenotype of fa/fa rats can be modified to some extent by the environment. Thus fa/fa rats become even more obese when offered a palatable, high-caloric diet rather than chow, whereas chow-fed fa/fa rats develop an improved muscle-to-fat-ratio and show improved health when they are subjected to exercise. Thus even the phenotype of animals homozygous for the fa mutation can be modified to some extent by the environment. By comparison, rats carrying one allele affected with this mutation, which is formally classified as recessive, seem particularly sensitive to environmental influences (Fig. 3, A and B). These heterozygotes (+/fa) develop a nearly normal body fat content under standard rearing conditions, but overnutrition during suckling age results in pups nearly as obese and unresponsive to leptin as normally reared fa/fa pups, whereas the consequences of the same treatment are much less severe for wild-type pups (15). It remains, however, to be clarified to what extent this pronounced gene-environment interaction observed in preweaned animals will persist into adulthood.

Although Wistar rats do not carry a known obesity-promoting gene, they demonstrate lifelong metabolic abnormalities as the consequence of early postnatal overnutrition (see Fig. 3C and further studies by A. Plagemann and colleagues, referenced in Refs. 6, 9, 14, and 15). Similarly, for some animal models with polygenically determined obesity or diabetes predispositions, lifelong consequences of interactions between early environmental impacts and genotype have been demonstrated (see Refs. 9 and 12). A critical point determining such lifelong consequences might be the quantity and quality of nutrition and exercise (“lifestyle”) in adulthood, which again depends on genetic predispositions. For example, it has been suggested by Maher et al. that +/fa rats have a higher susceptibility for obesity than +/+ rats when provided with high-caloric food from young adulthood onward (cited in Ref. 15). However, studies on potential interactions of these dietary changes in adulthood with pre- or early postnatal nutritional influences are still lacking.

Developmental (mal)programming of central nervous regulatory systems. Twenty-five years ago, the endocrinologist Günter Dörner put forward a hypothesis that proved particularly stimulating for attempts to elucidate potential mechanisms underlying modulations of the phenotype by environ-

![Diagram of leptin receptor gene and environmental impact](http://physiologyonline.physiology.org/)

**FIGURE 2.** The “road” from an identified genotype to the corresponding physiological function shown here for the example of one of the splice variants of the intact leptin receptor gene (Lepr<sup>+</sup>), the centrally expressed signaling receptor (LEPR<sub>rb</sub>). The function of the (normal or mutated) gene needs to be tracked from synthesis of the (functional or defective) receptor molecule and the subsequent cellular effects, through the intervening nervous and hormonal changes, to the resulting changes in energy uptake and dissipation, which are ultimately the causes for leanness or obesity. At all levels of this functional chain, modulating impacts of the environment are possible, as indicated by a few examples. (For further details see Refs. 1, 7, 15, 17, and work cited in Ref. 13).
Early postnatal overnutrition can precipitate excessive fat deposition and leptin resistance in a normally inconspicuous genotype, the heterozygous (+/fa) Zucker rat, whereas the same environmental impact has less severe consequences in wild-type (+/+ ) animals (data derived from Ref. 15). In Wistar rats, a strain without identified genetic lesion but known to be particularly prone to early environmental manipulations, rearing in small litters leads to lifelong increased growth and metabolic disturbances [data from Plagemann et al. (1999), cited in Ref. 13]. Overnutrition was established by rearing in small litters (i.e., only 3–4 pups/litter) compared with normal litters (i.e., 10–12 pups/litter) from postnatal day 3 to 21. A: although in normal Zucker rat litters only a very weak phenotypic difference occurs between +/fa and +/+ pups, rearing in small litters causes a much greater increase in size (carcass mass) and body fat content (fat) in +/fa pups (dashed lines) than in +/+ pups (solid lines) at weaning (on day 21). B: in normal Zucker rat litters, body fat content of +/+ and +/fa pups is similar, and both respond to treatment with recombinant leptin (white bars) from day 1 through 21 with a pronounced decrease in body fat content relative to their controls (dark bars). When reared in small litters, body fat content of +/fa pups is much larger than that of +/+ pups and their response to leptin treatment is nearly abolished. C: adult Wistar rats reared in small litters but normally fed (chow ad libitum) from weaning show several abnormalities typical for syndrome X compared with adults from normal litters. A suggested that, during critical periods of ontogeny, parts of the brain involved in the regulation of a hormone or a homeostatic variable might be sensitive to the corresponding hormone’s concentration. This implies that non-physiological concentrations during these periods might cause permanent malprogramming of the developing neuroendocrine control system, a premise that has been confirmed subsequently by many studies (discussed in Refs. 5 and 11). In particular, permanent effects of abnormal concentrations experienced in early development were demonstrated for steroid hormones, stress hormones, and insulin. Moreover, cases of nongenomic transmission across several generations resulting from maternal influences on the offspring and causing changes in central control circuits have been repeatedly reported, particularly with respect to disturbances of glucose tolerance (reviewed in Refs. 6 and 9) and to stress responses by the group of M. J. Meaney.

Impressive examples of direct and indirect changes of fetal or early postnatal insulinemia with long-lasting consequences for adult body weight and the expression of syndrome X-like abnormalities have been presented in epidemiological as well as experimental studies (6, 10). Epidemiological studies have shown much larger diabetes and obesity risks of children born to mothers suffering from diabetes during pregnancy vs. those of mothers developing the disease only after pregnancy (studies by D. Petit, discussed in Ref. 6). Experimentally, the interactions of genetic and environmental predisposition have recently become a focal point in this field of research. Thus the interaction between early postparturitional maternal influences and obesity- and/or diabetes-predisposing chromosomal regions in the offspring has been documented in one study on mice in which cross-fostering suggests the postnatal transmission of the maternal influence (12). In a strain genetically susceptible to diet-induced obesity, maternal overnutrition during gestation was reported to intensify the lifelong obesity disposition of the offspring, thereby revealing pronounced interactions between early environmental and genetic programming of energy balance regulation (discussed in Ref. 9).

Apart from appropriate nutritional factors, features of the early thermal environment, particularly occasional cold exposure, seem to be essential for the normal development and maintenance of thermoregulatory functions as well as the maintenance of body energy stores within an optimal range (for reviews, see Refs. 13 and 16). Even the thermal environment experienced prenatally, i.e., conveyed by the maternal system, seems effective in permanently programming the developing control system and may, thereby, determine thermoregulatory performance and energy balance regulation throughout life (16). There are several older reports on the effects of the early thermal environment on thermoregulatory responses differing profoundly by their long persistence from those elicited by similar thermal experiences in later life (see, for example, Fig. 4C). Attempts to identify central nervous changes that might mediate these effects have failed (discussed in Ref. 13). Current interest in mechanisms of body weight regulation and in programming effects of the early environment on this regulatory system has revived attention to these abandoned research fields. As an example, the effects of changing the thermal environment on body fat content and leptin responsiveness during suckling age are presented in Fig. 4, A and B. The results from the old thermophysiological studies combined with recent knowledge about the control of nutrient balance has stimulated hypotheses proposing that changes in the organization of the central sympathetic system might be the common mechanism underlying the programming by ther-
mal as well as by nutritional factors in the closely interrelated control systems of energy expenditure and fat storage (10, 13, 16).

**Environmental malprogramming of neural circuits controlling adiposity might not be limited to early developmental stages.** At any stage of its development, obesity has a strong tendency to persist and to cause secondary changes leading to its aggravation. Thus it appears plausible that an excessively positive energy balance and the hormonal changes associated with increased fat deposition during fetal life or suckling age have detrimental consequences. However, similar pathogenetic principles may well be effective later in life. In adult rodents, free access to high-caloric food is able to trigger massive obesity in sensitive strains that display quite normal body fat content when maintained on the standard, low-caloric laboratory chow, as shown in the studies of David West. Moreover, first exposure to high-caloric, hyperphagia-, and weight gain-inducing food may act as a programming event even in adult life, permanently shifting body weight (fat mass) control in sensitive animals to higher levels (9). In contrast to the effects of thermal experiences, programming of control circuits relevant for the control of body energy stores by nutritional factors might not be limited to a particular sensitive phase during early development. Similar to the programming in juveniles, a single bout of overnutrition in susceptible adults might cause nearly permanent shifts in body weight (fat mass) regulation in a way analogous to long-term learning. This intriguing idea, recently put forward by Barry Levin (9), is not yet supported by experimental evidence but provides an extremely promising target for further research.

**Potential mechanisms involved in developmental programming and their analogies in adults.** Although the concept of imprinting by stimuli experienced early in development has found widespread acceptance in the analysis of behavior and in developmental studies of sensory systems, the analogous idea of hormonal and metabolic programming (imprinting) has long been ignored until it was “newly” discovered recently (11), with public attention spreading even into popular magazines. To elucidate the underlying changes in the central nervous system, helpful experimental approaches may be offered by observations of seemingly permanent changes in the regulation of energy stores following the first confrontation with overfeeding and/or the first bout of diet-induced obesity, even if this happens in adulthood. The advantage provided by models of adult metabolic malprogramming is the possibility of studying neural circuits both before and during the environmental impact. Extending the analysis to animals known to be either prone or resistant to diet-induced obesity is particularly intriguing because it offers the possibility of comparing individuals before they are affected by secondary influences emerging from the change in diet and from developing obesity. With this approach, it was possible to show that characteristic metabolic or neuronal abnormalities exist before obesity starts to develop in rats prone to diet-induced obesity. Interestingly, some of these abnormalities seem to “normalize” after obesity has developed, such that the obesity-prone animals will now defend their increased fat stores as do starving normal animals (see citation in Ref. 9). Abnormalities in the central sympathetic system and in the regulation of neuropeptide Y expression in animals prone to obesity and associated metabolic disorders, regardless of whether the obesity is determined genetically or by early environmental impacts, currently represent the most consistently recognized feature of these central changes, although the findings in different animal models or under different experimental conditions do not yet fit a coherent picture (9, 10, 16).

**Neglect of details causes confusion**

Something is determined by the quantity of early nutrition, but what? Although there are numerous studies showing that

![Figure 4](http://physiologyonline.physiology.org/)

**FIGURE 4.** A: rearing at thermoneutrality (TN) from postnatal day 4 increases fat deposition and suppresses leptin responsiveness compared with cold-reared rat pups. B: severely impaired cold defense of these pups, which can be ameliorated by leptin treatment, is revealed by a short cold exposure at day 16. Data in A and B for artificially reared rat pups are from Stehling et al., 1997 cited in Ref. 13. Black bars and solid lines, leptin treatment (from postnatal day 7 to 16); white bars and dashed lines, saline treatment; fat, total body fat; ΣMR, total metabolic rate from day 7 to 16. C: lasting improvement of cold defense after juvenile cold exposure of rats. Although the effects of cold acclimation in adulthood vanish within 4 wk, severe cold exposure during suckling age caused a lasting improvement of cold defense, as demonstrated by a cold test (ambient temperature = 5°C) carried out 4 mo after the animals had been returned to 25°C. Tc, core temperature. Data derived from Doi and Kuroshima, cited in Ref. 13.
differences in body weight between animals from undernourished and overnourished litters persist into adulthood, it is often overlooked that there are only a few studies that actually document differences between normally reared and overnourished litters. Starting with the pioneering work by J. Hirsch’s group (e.g., see citation in Ref. 15), it has been repeatedly shown that rearing in large litters (i.e., in litters in which the number of pups greatly exceeds the number of teats) produces long-lasting changes in rodent adipose tissue morphology and function compared with those of pups reared in small litters (i.e., in litters in which the number of suckling pups was much smaller than the number of teats). This suggests the possibility that the observed lasting differences are more likely due to the consequences of postnatal restriction of food intake in undernourished litters than to the growth- and/or adiposity-enhancing effects of overnutrition. Several studies have demonstrated increased body size and altered metabolic parameters, although without specifying body fat content, in adult rats subjected to early postnatal overnutrition compared with normal nutrition (discussed in Refs. 6 and 10). In contrast, there are only three original papers on adult rodents in which the effects of postnatal overnutrition vs. normal nutrition specifically on adipose tissue are separated from those on general growth. Although one demonstrated an increase in fat mass relative to total body mass in mice (2), the other two yielded negative results in rats (see Ref. 4). It is therefore mandatory to discriminate carefully between growth, adiposity, and metabolic abnormalities as long-lasting consequences of early overnutrition.

Perspectives

In summary, there is no doubt that gene-environment interactions are crucial in determining predispositions for obesity and other complex metabolic disorders. However, obesity causes many secondary changes, making it difficult to identify its primary cause once it has developed. Thus there is great need for using experimental approaches permitting the separation of primary (causative) from secondary (aggravating) factors associated with obesity. Studying animals that are already obese obviates the greatest advantage that animal models offer for obesity research, namely the chance to identify the primary pathogenetic factors. Moreover, studying manifest obesity reduces the chances to find ways to prevent environmental impacts from triggering permanent epigenetic malprogramming in a regulatory system genetically programmed for controlling body fat content when food availability is limited and energetic costs are high. Keeping in mind that the ultimate cause of failure of body weight regulation might frequently be a genetic program not fitting the present environment, the postulate “to cure the environment” put forward by James O. Hill seems no more ambitious than the hope of identifying the (patho)physiological consequences of individual, multigenetically determined traits as a means to stop the obesity epidemic affecting ~200 million people worldwide (3, 8).

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