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Epigenetic Influences on Food Intake and Physical Activity Level: Review of Animal Studies

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Abstract

Epidemiological studies suggest that the perinatal environment can predispose human offspring to develop obesity and type 2 diabetes. Animal models provide a means of assessing the consequences of manipulating the perinatal environment in ways that cannot be done in humans. During the gestational period, maternal malnutrition, obesity, type 1 and type 2 diabetes, and psychological and pharmacological stressors can all promote, while early-onset exercise can ameliorate, offspring obesity and diabetes, especially in genetically predisposed offspring. Many of these perinatal manipulations are associated with reorganization of the central neural pathways which regulate food intake, energy expenditure, and storage in ways that enhance the development of obesity and diabetes in offspring. Both leptin and insulin have strong neurotrophic properties, so altered availability of either during the perinatal period can underlie some of these adverse developmental changes. Because perinatal manipulations can permanently alter the systems which regulate energy homeostasis, it behooves us to identify the responsible factors as a means of stemming the tide of the emerging worldwide obesity epidemic.

We are in the midst of an epidemic of childhood obesity in the developed world (1), and evidence points to both genetic and perinatal environmental contributions to this epidemic (2,3). Because it is difficult to control the many factors involved in these interactions in humans, animal models have served as reasonable surrogates. However, despite the important contributions of the brain to the control of energy homeostasis, few animal studies have assessed the impact of the interactions of genetic background and the perinatal environment on the development of the neural pathways involved in these control mechanisms. Energy homeostasis, the balance among energy intake, expenditure, and storage, is regulated by a constant dialogue between the brain and body. Hard-wired afferents from peripheral organs, hormones, peptides, and metabolites all converge upon specialized metabolic sensing neurons which are arrayed throughout the brain in an interconnected, distributed network (4). These afferent signals are integrated by these specialized neurons to alter their membrane potential and firing rate as a means of regulating the various downstream systems which control intake, assimilation, and expenditure of energy. Leptin and insulin are two important hormonal signals which are secreted into the bloodstream in proportion to the amount of adipose tissue (5). They are transported across the blood–brain barrier and interact with metabolic sensing neurons such as those in the arcuate nucleus of the hypothalamus (ARC), which synthesize and release neuropeptide Y (NPY) and agouti-related peptide (AgRP) and proopiomelanocortin (POMC) (6,7,8,9). NPY released from these neurons interacts with receptors in the paraventricular

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nucleus (PVN) and lateral hypothalamic area (LHA) to increase food intake and reduce energy expenditure. POMC neurons release alpha-melanocyte-stimulating hormone (α-MSH), which acts in the PVN and LHA on melanocortin receptors to decrease intake and increase expenditure. Finally, AgRP released from ARC NPY/AgRP neurons acts as a functional antagonist of α-MSH at its melanocortin receptors (7). When adipose stores rise, leptin and insulin levels rise and inhibit NPY/AgRP and activate POMC neurons, providing a negative feedback system to inhibit intake and prevent obesity (9). In addition to their critical role in regulating energy homeostasis, leptin and insulin are also critical mediators of neural development during the pre- and postnatal periods (10,11,12,13). Thus, many studies of perinatal influences on the development of obesity have focused on these two hormones.

Animal Models and the Study of Perinatal Influences on Obesity

There are several ways in which environmental perturbations can affect outcomes in developing animals. First, there can be modification of existing genes (i.e., epigenetic effects). This is exemplified by effects of both dietary and behavioral manipulations during the postpartum period upon gene expression through changes in gene methylation (14,15). This mechanism may explain why there can be such a wide variation in body weight and adiposity among inbred strains of mice (16,17).

Another way in which perinatal factors can affect offspring obesity is to alter the development of the neural pathways involved in the regulation of energy homeostasis. To study these factors, we selectively bred rats prone to develop diet-induced obesity (DIO) and those prone to be diet-resistant (DR) from the outbred Charles River Sprague–Dawley strain (18). Selectively bred DIO rats overeat and become obese over 3–4 weeks on a 31% fat diet, while DR rats quickly adjust for the increased caloric density of the diet and remain lean (19,20). Once they become obese, DIO rats defend their higher body weight and adiposity against long periods of caloric restriction in that they quickly return to their higher pre-restriction levels when allowed to eat *ad libitum*, even on low-fat (5%) chow (21). The similarity to human obesity, approximately two-thirds of which is due to a polygenic mode of inheritance (22), was established by showing that the DIO phenotype was maintained when DIO males were bred against obesity-resistant Fisher F344 dams to produce the F.DIO strain (23). An important characteristic of DIO rats is that they are born with central resistance to the anorectic and thermogenic effects of leptin (13,20,24,25). It appears that their leptin resistance is due to a reduced number of available leptin receptors in the ARC and other hypothalamic nuclei (13, 20,24,26). In addition, DIO rats have reduced anorectic responses to central insulin infusions associated with decreased insulin receptors in the ARC before they become obese (5,26). Finally, DIO rats also have reduced responsiveness to glucose (27). Thus, these DIO rats have a raised threshold for sensing and responding to a number of hormonal and metabolic signals from the periphery which should inhibit intake and stimulate thermogenesis as adipose stores and plasma glucose levels rise. This raised threshold is likely a major predisposing cause of their development of obesity on high-fat diets. In addition, since leptin is required for the normal development of hypothalamic pathways involved in energy homeostasis regulation (28), the reduced leptin sensitivity of DIO rats appears to underlie their abnormal development of these pathways (13,29,30,31).

Perinatal Factors Alter Genetic Predisposition to Obesity

While maternal undernutrition can lead to offspring obesity in rodents (32,33) and humans (2), maternal overnutrition is likely to be a more important problem in the developed world. Maternal obesity throughout gestation and lactation resulting from high fat intake produces offspring obesity in outbred rats (34). However, in our DIO/DR model, only those offspring with the DIO genotype become more obese as adults when their dams are made obese

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throughout gestation and lactation, even when those offspring are fed only a low-fat diet from weaning (35). Importantly, these obese DIO offspring have abnormal development of important monoamine pathways which influence the development and function of hypothalamic pathways involved in energy homeostasis (36,37). Thus maternal obesity influences neural development adversely, specifically in animals which are genetically predisposed to become obese. Similarly, maternal obesity during gestation and lactation predisposes offspring of obesity-prone F.DIO rats to become obese as adults, but so does maternal caloric restriction and exposure of dams to corticosteroids during the third week of pregnancy (38). Thus, a variety of perinatal manipulations can accentuate the propensity of genetically predisposed animals to become more obese as adults.

Of greater concern is the finding that an obesogenic postnatal environment can make even obesity-resistant offspring obese as adults. While maternal obesity throughout gestation and lactation does not predispose DR offspring to become obese as adults (35), cross-fostering DR pups to obese DIO dams on the second day of life causes them to become obese as adults when exposed to a high-fat diet (39). Unfortunately, the opposite does not hold. Cross-fostering DIO pups to lean DR dams does not reduce their predisposition to become obese on high-fat diets as adults (39). This adverse effect on DR pups weaned with obese DIO dams may be due to the extremely low levels of poly- and monounsaturated fatty acids and very high levels of insulin in the milk of those dams as compared to the milk of lean DIO and DR dams (39). These fatty acids are essential for normal brain development (40), and insulin is an important factor in the development of hypothalamic pathways which, in excess, can cause major abnormalities associated with the development of obesity (12).

Early-Onset Exercise Prevents the Development of Obesity

The news is not all bad, however. Even though DIO rats run only half as much as DR rats, exercise in a running wheel selectively produces weight and fat loss only in DIO rats (41,42). Because the brain continues its development well into adolescence, we postulated that early-onset exercise might protect DIO pups from becoming obese by altering the signaling pathways involved in the regulation of energy homeostasis. In fact, post-weaning access to running wheels does prevent DIO pups from becoming obese, even when fed a high-fat diet. More importantly, only 3 weeks of exercise is sufficient to prevent them from becoming obese for up to 10 weeks (~2 to 3 years of human life) after the wheels are removed (41). Such a sustained effect of exercise does not occur in adult rats (43) suggesting that early-onset exercise does, indeed, affect brain development during this vulnerable period. Our preliminary data suggest that the sustained obesity resistance conferred by early-onset exercise in DIO rats is associated with a persistent increase in central leptin sensitivity (unpublished data). Of equal importance is the finding that when sedentary DIO pups on a 31% fat diet were calorically restricted to match their weights to those of the exercising pups for 6 weeks, they became more obese as adults once they were allowed to eat *ad libitum* (41). Thus, early-onset exercise ameliorates, while early-onset caloric restriction accentuates, the development of obesity in genetically predisposed rats. These studies emphasize the importance of the juvenile period of development during which dietary and exercise interventions can have long-lasting effects that alter the development of obesity in obesity-prone individuals.

Conclusions

The use of animal models allows us to control critical variables to assess the important interactions among genetic background, perinatal factors, and the development of neural pathways which control the regulation of energy homeostasis. Studies in models such as DIO and DR rats demonstrate that the multiplicity of factors involved are dependent on both the timing and the genetic template upon which they act to promote or attenuate the development

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of obesity. While many factors promote the development of offspring obesity, even when there is an obesity-resistant genotype, early-onset exercise appears to be the one factor which has a long-lasting and selective effect on reducing the propensity of DIO offspring to become obese. There is now good evidence that such interventions can have long-lasting effects on the development, structure, and function of the neural pathways involved in the regulation of energy expenditure. Since it is unlikely that our genetic makeup has changed in the last few decades, such studies suggest that we should focus on such early life factors as a possible explanation for the recent increase in childhood and adult obesity in humans. The hope is that identification of such factors will lead to therapeutic interventions which will stem the obesity epidemic now sweeping the developed world.

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