MINI REVIEW

The Obesity Epidemic: Metabolic Imprinting on Genetically Susceptible Neural Circuits

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Abstract

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The apparent obesity epidemic in the industrialized world is not explained completely by increased food intake or decreased energy expenditure. Once obesity develops in genetically predisposed individuals, their obese body weight is avidly defended against chronic caloric restriction. In animals genetically predisposed toward obesity, there are multiple abnormalities of neural function that prime them to become obese when dietary caloric density and quantity are raised. Once obesity is fully developed, these abnormalities largely disappear. This suggests that obesity might be the normal state for such individuals. Formation of new neural circuits involved in energy homeostasis might underlie the near permanence of the obese body weight. Such neural plasticity can occur during both nervous system development and in adult life. Maternal diabetes, obesity, and undernutrition have all been associated with obesity in the offspring of such mothers, especially in genetically predisposed individuals. Altered brain neural circuitry and function often accompanies such obesity. This enhanced obesity may then be passed on to subsequent generations in a feed-forward, upward spiral of increasing body weight across generations. Such findings suggest a form of "metabolic imprinting" upon genetically predisposed neural circuits involved in energy homeostasis. Centrally acting drugs used for obesity treatment lower the defended body weight and alter the function of neural pathways involved in energy homeostasis. But they generally have no permanent effect on body weight or neural function. Thus, early identification of obesity-prone mothers, infants, and adults and treatment of early obesity may be the only way to prevent the formation of permanent neural connections that promote and perpetuate obesity in genetically predisposed individuals.

Key words: diet-induced obesity, neuropeptide Y, neural development, insulin, neural plasticity, POMC

Introduction

Obesity has reached epidemic proportions in the developed countries of the world (1). This phenomenon is frequently ascribed to the combination of excess consumption and decreased physical activity. However, there may be less obvious but more important reasons. Genetic predisposition for obesity, the so-called "thrifty genes" (2,3), may underlie the greater metabolic efficiency and increased weight gain of some individuals. The hypothesis of this review is that a genetic predisposition and the metabolic consequences of a state of positive energy balance interact to physically modify the neural systems that control energy homeostasis. Because some new neural connections are more easily formed than abolished, such "metabolic imprinting" (4) on critical neural pathways might additively raise the defended level of body weight. Although the mechanism remains unclear, this modified neural coding might be passed on to succeeding generations because of the resultant metabolic alterations produced in the maternal environment of obese mothers during gestation and weaning (5,6). Through such a feed-forward cycle, obesity would beget further obesity in a continually upwardly moving spiral. Thus, neural plasticity may be an important contributor to the perpetuation of obesity during both development and adulthood. Although many organ systems may be affected by metabolic imprinting (4), this review will focus only on the effects of such imprinting on the nervous system.

Perinatal Interactions between the Maternal Environment and Genetic Background

Because brain development continues well into the first years of life, both the intrauterine and postnatal environments are critical determinants of the physiological, metabolic, and neural development of pathways regulating energy homeostasis. Neural development consists of neuronal

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differentiation, migration of neurons, axon outgrowth and target attachment, synapse formation, and removal of neurons that fail to reach appropriate targets. Several maternal conditions have been linked to obesity in both human and rodent offspring, and these, in turn, have been shown to affect neural development. Paradoxically, both maternal caloric deprivation (7,8) and maternal obesity (9) produce obese offspring. Similarly, mothers with both type I (10–12) and type II (9,13) diabetes tend to have obese progeny. Finally, both excess intake (14) and exposure of neonates to exogenous insulin during the postnatal period (15,16) lead to obesity. Some of these apparently conflicting findings may be explained by the timing of the respective perturbations in relationship to critical milestones in the development of the nervous system as well as the genetic background of the mother (9).

Insulin and the family of insulin-like growth factors may play a critical role underlying the development of obesity in offspring. Exogenous insulin administration to the dam during the third week of gestation (17,18) or to pups during the first two postnatal weeks (19–22) results in obese offspring. Insulin and the insulin-like growth factors affect neuronal differentiation (23) and survival (24), neurite formation (25), synaptic transmission (26), and α_2-adrenoceptor density (27). Maternal insulin injections produce obese offspring that have increased noradrenergic innervation and increased norepinephrine release in the ventrobasal hypothalamus (18). Manipulations of insulin levels during gestation and the early postnatal period produce obese offspring with altered neuronal size and numbers in hypothalamic nuclei, which play critical roles in energy homeostasis (10–12,20,28–32). It remains to be shown whether these changes in morphology are cause or effect of the obesity and abnormal glucose metabolism that accompany them. Besides insulin, there are many other metabolic abnormalities associated with maternal obesity that are likely to enhance obesity in offspring. The process of metabolic imprinting on genetically susceptible individuals during development might potentially create a vicious cycle whereby obesity is increased in each succeeding generation (5). As each generation of mothers became increasingly obese, the metabolic consequences of that obesity could have an escalating impact on neural changes that promote obesity. Such a feed-forward system would produce an upward spiral of obesity prevalence in the population. This might explain why the youngest cohort of adults (18–29 year olds) has shown the greatest increase in the prevalence of obesity (1).

Adult Dietary and Metabolic Exposures Alter Neural Circuitry and Perpetuate Obesity in Predisposed Individuals

Little is known of the factors that predispose individual humans to become obese. Neither do we understand the cause and effect relationship between obesity and abnormalities of neural function found in some obese humans. First, it is virtually impossible to identify an obesity-prone human before they become obese and develop the metabolic consequences of obesity. Second, the study of function in small, anatomically specific regions of the human brain is only in its infancy (33,34). We still have no reliable way to assess the myriad central neurotransmitter and peptide systems involved in body weight regulation in humans. Thus, animal models have been used as surrogates. Although single gene mutations producing obesity in rodents provide interesting insights, the early onset of obesity in such models introduces the same cause-effect conundrum seen in human obesity. On the other hand, it is possible to examine obesity-prone and obesity-resistant individuals in the rat model of diet-induced obesity (DIO). In this model, about half of a given strain of outbred rats becomes obese only when placed on diets of relatively high energy density (35–39). The rest are diet-resistant (DR) and remain lean on such diets. Importantly, obesity-prone and -resistant rats can be identified prospectively before they express their respective phenotypes (36,40–43). This provides important insights into defects that might predispose rats to become obese. Furthermore, substrains of DIO and DR rats now have been selectively bred (37). This allows manipulation of the prenatal and early postnatal environment so as to alter neural and metabolic function in rats of a precisely known phenotype or, perhaps, genotype. Such studies suggest that DIO is inherited as a polygenic trait similar to much of human obesity (44).

The DIO model manifests a number of abnormalities in neural function in the obesity-prone rat that antedate the onset of obesity. Many of these are "normalized" to DR levels when obesity becomes fully developed after exposure to a high energy diet. Coincident with such normalization of neural function, fully obese DIO rats defend their higher body weight and adiposity against both over- and underfeeding (38,39,45). It is a common experience that most obese humans and rats gradually move upward and defend higher body weights but rarely defend lower body weights imposed by dieting. In rats and humans, successively higher weights are defended against both short and long term over- and underfeeding (B. E. Levin, unpublished data) (38,45–47). The formation of new synaptic connections in genetically predisposed individuals exposed to high energy diets and/or maternal obesity might underlie this upward trajectory of body weight. Once a given synaptic connection is formed, it is strengthened by repeated use and rendered near permanent through gene induction, synthesis of new proteins, axonal and dendritic proliferation, and the formation of synaptic contacts. Such a process is thought to underlie the formation of long term memories (48)and the reorganization of circuits following neural injury (49,50). Importantly, these processes are modulated by neurotransmitters such as norepinephrine (49) and peptides such as insulin (25,27,51), the functions of which are altered in obesity-

prone animals (17,18,35,36,40,42,52–54). Thus, the action of metabolic factors on genetically programmed neural functions might constantly move the body weight set-point in an upward direction as the individual chronically consumed more calories. Once formed, these new connections would be difficult to remove and body weight would move only in one direction—upward. It is important to point out that there are no firm data that demonstrate the formation of such permanent neural connections during the development of obesity. We have found that offspring of obese DIO dams become more obese as adults (9) and have a selective reduction in noradrenergic innervation of the paraventricular nucleus compared to offspring of DIO dams kept lean during gestation (B. E. Levin, unpublished data). Also, adult DIO rats have a reduced number of axonal synapses on hypothalamic arcuate nucleus (ARC) neuronal cell bodies after 2 weeks on high energy diet (T. L. Horvath and B. E. Levin, unpublished data). There is also clear evidence that brain α_2-adrenoceptor binding is permanently altered when DIO and DR rats are moved through cycles of moderate and low fat diets (55).

One example of plasticity of neural function involves the changes in ARC neuropeptide Y (NPY) expression seen during the development of DIO. NPY is a major anabolic neuropeptide in the brain (56–58). Central NPY injections increase food intake (56) and reduce the oxidation of dietary fat (58) as is known to occur during the development of DIO in rats (59) and in some obese humans (60). This should favor increased fat deposition when dietary fat intake is increased. The ARC NPY neurons appear to be largely responsible for these metabolic effects of centrally administered NPY (39,43,61). As in obese Zucker rats (62) and *ob/ob* mice (63), the obesity-prone rat overexpresses ARC NPY mRNA (39,43). This overexpression and concomitant dysregulation are corrected when obesity-prone rats develop full-blown DIO (39,64). They then avidly defend their new elevated obese body weights against both short and long term energy restriction or overfeeding (38,39,45) (B. E. Levin, unpublished data). Thus, this genetically programmed NPY overexpression should make obesity-prone rats more metabolically efficient and prime them to become obese when provided with an obesity-promoting diet (55). In effect, the development of obesity appears to be the preprogrammed state that DIO animals must reach if this neuropeptide system is to function normally.

There are several other examples of abnormal neural functions in obesity-prone rats that are "normalized" (compared to DR rats) when obesity becomes fully developed. These include reduced numbers of forebrain α_2-adrenoceptors (52,65), abnormal hypothalamic norepinephrine turnover (42,66), abnormalities of neuronal glucosensing (67–71), and reduced neuronal activity in the ventromedial nucleus (72,73). As with NPY, many of these dysfunctional systems may prime DIO rats to become obese when provided with adequate dietary exposure. Once altered by the development of obesity, these "normalized" systems might play an integral role in the defense of the new, higher body weight. To date, no studies clearly demonstrate that such changes in neural function in response to the metabolic perturbations associated with the development of obesity are due to alterations in neural circuits as opposed to altered expression of the transmitters and peptides involved in energy homeostasis.

In fact, no definitive cause and effect relationship between changes in brain function or changes in neural circuitry and the development of obesity has ever been shown. Brain lesion studies originally led to the conclusion that the brain was involved in the defense of energy homeostasis. Large lesions of the ventrobasalar hypothalamus produce obesity (74,75), whereas lesions of the lateral hypothalamus result in lower body weight (42,76,77). Once the new body weights are established, rats with lateral hypothalamic lesions avidly and appropriately defend their lower body weight (78). It is less clear that animals with ventrobasalar hypothalamic lesions, which typically involve the ARC (74), defend their higher body weight as avidly (76,79).

However, such studies do support the idea that neural elements in the ARC are critical to the control of energy homeostasis. This does not preclude a role for other brain areas; it simply reinforces the importance of this specific brain region. Neurons in the ARC monitor a host of signals from the periphery and surrounding brain that carry information about the metabolic status of the body (80). Both ARC NPY and pro-opiomelanocortin (POMC) neurons contain mechanisms for monitoring peripheral levels of insulin (81), leptin (82), and glucose (71,80,83,84). Such neurons form an integral link in the circuitry involved in autonomic and pituitary function (85–87). Thus, they represent a special class of integrator-effector neurons that monitor and integrate metabolic and neural signals from the periphery and brain. Their integrated information is sent forward to effector areas that modulate the function of various systems involved in energy homeostasis (80). Such integrator-effector neurons represent a likely interface between genetic background and the environment in determining the level of defended body weight.

What Limits the Efficacy of Obesity Therapy?

Currently available, centrally acting drugs like fenfluramine or sibutramine produce no more than an average of 10% to 15% reduction in body weight (88–91). Such drug-induced reductions in body weight are then defended against both under- and overfeeding (91). The signals and receptor systems responsible for this lowering of the defended body weight are unknown. Most likely the metabolic consequences of altering body

weight and carcass composition interact with the entire integrated neural system that regulates energy homeostasis. Given the critical nature of energy homeostasis for the survival of the individual and the species as a whole, it is not surprising that such a system would be complex, redundant, and extremely plastic (92). We have found that ARC NPY and POMC neurons are reset during chronic sibutramine treatment. Thus, despite a 15% decrease in body weight, sibutramine-treated rats have normal expression of these peptides, whereas vehicle-treated rats that are food-restricted to produce a similar weight loss show the expected increase in NPY and decrease in POMC mRNA expression seen with energy deficit (93). Thus, it is likely that additional drugs and/or other therapies that target other parts of the central and peripheral energy homeostasis pathways will need to be used in combination with drugs like sibutramine and fenfluramine to effect additional, sustained weight loss.

Summary and Conclusions

It is the hypothesis of this review that neural plasticity plays an important role in establishing the defended level of body weight and energy homeostasis. The brain is the likely command center that coordinates such regulation. As such, it requires adequate information about the function, capacity, and content of various fuel storage depots. During both brain development and adult life, the metabolic and neural sources of such information can act both as signals and as instruments of change in the very neural circuits that monitor and regulate them. Such metabolically imprinted neural circuits can develop a long term stability that defies reversal. There appear to be certain individuals who are genetically predisposed toward such neural-metabolic interactions. This plastic change could produce a feed-forward cycle of increasing obesity in succeeding generations. This would increase the prevalence of obesity in the population as a whole. This construct is primarily hypothetical but is testable through experiments that directly examine the formation of new synapses and permanence of functional neuronal connections in obesity-prone animals during development and adult life. If correct, this hypothesis has important implications for the way in which we approach the problem of obesity. Because so much of brain plasticity occurs during the perinatal period, identification and management of those metabolic factors that magnify and perpetuate the development of obesity in offspring should be a primary goal of obesity prevention. In adults, it is unlikely that we will be able to dismantle the permanent changes in neural circuitry wrought by the interaction of genes and environment once they are established. Instead, treatment for the already obese will likely require life-long treatments that affect several of the systems controlling energy homeostasis simultaneously.

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