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MINIREVIEW

Evidence for a Central Mechanism of Obesity in the Zucker Fatty Rat (*fa/fa*) (42380)

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Considerable attention has been given toward identifying the etiological factors of obesity. In particular, the genetic component has been considered an important determinant of body morphology, i.e., body fatness. Recently an extensive clinical report on adoptees has further substantiated a strong correlation of genetic background with body weight and obesity (1). Experimental evidence has also emphasized the significance in genetic profile for studying the etiology of obesity. Accordingly the Zucker "fatty" rat has been frequently employed as a genetic model for such investigation.

The development of obesity has been shown to be a complicated process which involved metabolic alterations in various organs of the body. Over the past several years the metabolic and endocrine pattern of development of obesity in the Zucker fatty rat has been characterized. Evidence will be presented to demonstrate that abnormal central nervous system (CNS) function is the most likely explanation for a number of peripheral tissue metabolic changes that occur during the development of this, theoretically simple, form of obesity, the single *fa* gene mutation.

Energy Partitioning. Many of the initial studies with the Zucker rat were designed to determine the pattern of nutrient utilization under conditions in which hyperphagia was not a confounding factor of the obesity. In these early studies it was shown that when energy and protein intake of the Zucker fatty rat was paired to that of the lean rats there was a defect in the partitioning of both energy and protein (2, 3). On the same amount of dietary energy, the obese rat appeared to be twice as efficient as the lean in depositing energy in fat stores. On the other hand, efficiency of protein utilization was decreased in the obese rat resulting in a reduction in body protein. In order to determine the mechanism involved in energy and protein partitioning, metabolic patterns in individual organs were examined.

Peripheral Organs Effected by the *fa* Gene. *Adipose tissue.* The most obvious organ influenced by the *fa* gene is adipose tissue. Initially this organ received a lot of attention in the study of obesity (4, 5). These studies showed that there was no impairment in the release of fatty acids from adipose cells. The rate of *de novo* lipogenesis was increased and the enzymes involved in the synthesis of fatty acids from glucose were elevated especially during the early stages of the obesity (6–9). The *fa* gene stimulation of lipogenesis was found to be effective throughout the 24-hr cycle and did not show a diurnal rhythm found in their lean littermates (10). The level of lipoprotein lipase was shown to be elevated and was proposed to be the primary cause of the obesity (11). However this hypothesis has since been challenged (12, 13). The type of adipose cellular growth in this form of obesity was found to involve both hyperplasia and hypertrophy (14–17). While these studies provide some information of the final common pathway for excessive lipid deposition in the Zucker fatty rat, there was no evidence that the primary genetic defect occurred in this tissue.

Hepatocytes. The mechanism of increased lipid deposition could have involved increased rates of *de novo* lipogenesis in hepatocytes and subsequent transport of these lipids to adipose tissue. It was shown that serum lipids and lipoprotein production by the hepatocytes were elevated (18, 19). *In vivo* hepatocyte lipogenesis and hepatic lipogenic enzymes were elevated several fold, even when the obese animals were pair-fed to the control animals (20–23). If stimulation of hepatic lipogenesis caused the obesity and was driven by a gene product such as hepatocyte fatty acid synthetase, then by feeding the rats a high fat diet this enzyme should have been inhibited and

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should have prevented the development of obesity. However this did not occur. The enzyme was effectively inhibited, but the obese rat continued to deposit excessive amounts of body fat (23). Therefore, elevated hepatocyte lipogenesis was a secondary event in the development of Zucker fatty.

An alternate hepatocyte mechanism for increasing the amount of fatty acids available for deposition in adipocytes would be through decreased fatty acid oxidation. Isolated hepatocytes from fatty rats were found to be less capable of oxidizing fatty acids than those from controls (24–26). Since the uptake of fatty acids by cells from both genotypes was similar, the fate of the fatty acids was different. The cells from the obese rats partitioned fatty acids more toward triglyceride synthesis and less toward oxidation.

Others have reported differences in hepatocyte oxidation and ketogenesis in the Zucker rat (19, 27). It was concluded that it was the endocrine status of the obese rat that stimulated greater rates of fatty acid synthesis which acted to inhibit oxidation through malonyl CoA and led to the enlargement of adipose tissues through an enhanced rate of triglyceride synthesis and secretion.

Muscle and bone tissue. Nitrogen balance studies of the Zucker rat showed that when given the same amounts of dietary protein, the obese rat tended to deposit amino acid carbon skeletons in the form of fat, rather than muscle protein (2, 3). Studies on the development of muscle tissue under conditions of controlled protein and energy intake, showed that the development of muscle tissue was impaired (28). Skeletal muscle DNA, RNA, and RNA/DNA ratios were decreased in the gastrocnemius muscle of obese rats. In addition, tibias and femurs were shown to be one-third lighter and shorter in the obese than in the lean rats (28). Bone mineralization was also impaired in obese animals (29).

Amino acid metabolism has been shown to be significantly altered in the Zucker fatty rat. Reduced protein synthesis and increased amino acid catabolism resulted in less nitrogen deposition (3, 28, 30). Other studies have shown that muscle tissue development and metabolism were effected by the *fa* gene (31–34). It was apparent from these studies that there were multiple metabolic alterations in muscle that could not be caused by a single gene product change in this tissue. A more plausible explanation was that the endocrine status was altered by the *fa* gene (i.e., decreased growth hormone, somatomedin activity, and elevated corticosterone) and that this endocrine profile led to the secondary changes in muscle and bone tissue (35, 36).

Brown adipose tissue (BAT). Defective brown adipose tissue metabolism has been proposed as a mechanism for the increased energetic efficiency of lipid deposition in a number of animal models of obesity. These include dietary-induced obesities, hypothalamic-induced obesities, and a number of genetic-induced obesities (37). Because of the number of defects in BAT that have been reported in different types of obesity it appears that a defect in this organ may facilitate the development of obesity but does not appear to be a primary defect. In our studies with Zucker rats we found that decreased spontaneous activity on exposure to acute cold as early as 3 days was not mirrored, at that age, by changes in brown adipose tissue histochemistry (16). In addition, palmitate oxidation by brown adipose tissue in both basal and norepinephrine stimulated condition, was the same in lean and Zucker fatty rats (38).

Although there has been a substantial commitment to the study of BAT mechanisms, it appeared that those investigators extensively working in the BAT area were becoming more cautious about the role played by BAT in the development of obesity. The French workers Bazin *et al.* (39) studied the guanosine diphosphate (GDP) binding of very young Zucker rats and stated that they "were not able to demonstrate the presence of a decreased GDP binding independently of an increased fat content. . . ." Stern *et al.* (40) suggested that "the mechanism for the different (BAT) response may reflect differences in the effectiveness of the sympathetic nervous system to elicit tropic responses from BAT and/or the central nervous system to evoke such responses." Levin *et al.* (41) also indicated a secondary role for BAT, "abnormalities in neurohumoral regulation could then lead to the many peripheral defects that have been demonstrated in this animal (*fa/fa*)." Finally,

Himms-Hagen (37), who has an extensive background in BAT research, concluded in a recent publication on the Zucker rat that "the most probable defect is suggested to be associated with the hypothalamus."

Central Nervous System Regulation of Obesity in the Zucker Rat. From the above description it can be concluded that a number of peripheral modifications occur to facilitate the pattern and efficiency of energy and protein deposition in the Zucker fatty rat. The coordination of these various tissues and functions is under the control of the central nervous system. Therefore, it is probable that the primary genetic defect is in some central nervous system (CNS) function. Evidence that supports this conclusion is discussed below.

1. Defective hypothalamic mechanisms for food intake regulation. Parabiosis techniques have been used to identify the role of circulating factors in the development of obesity (42). When Zucker rats were parabiosed it appeared that the obese rats generated a humoral satiety factor that they did not respond to, but that could be recognized by their lean parabiotic partners (43). It was suggested that the abnormality in the fatty rat could lie in the reception of, or in the hypothalamic response to, serum satiety factor.

The lateral, ventromedial, and paraventricular areas of the hypothalamus have been shown to be primarily involved in feeding behavior (44–46). The level and pattern of food intake as well as diet selection have been shown to be significantly altered in the Zucker fatty rat (47–50). Glucoprivic feeding was stimulated by application of the glucose antimetabolite 2-deoxyglucose to the CNS, and in particular to the area postrema (51). The Zucker fatty rat had an impaired response to this antimetabolite (52), suggesting a defective CNS metabolic mechanism in this animal.

Metabolic activity within selective brain sites has been shown to be influenced by feeding status and level of satiety in the normal rat (53). Glucose flux through the γ-aminobutyric acid (GABA) shunt pathway was 32% lower in the lateral hypothalamus of hungry rats than in their fed controls, whereas glucose flux through the pentose phosphate pathway was 152% higher in the ventromedial area of the hypothalamus of overfed, anorectic, rats. It was also shown that fatty acid oxidation in the lateral hypothalamus was influenced by feeding status of the rat (54). If these pathways reflect energy status in the normal rat, it is possible that the Zucker fatty rat has a hypothalamic metabolic abnormality that causes an inaccurate estimation of peripheral energy status and permits the fatty rat to overeat.

2. Defective hypothalamic control of the endocrine pancreas. The elevated level of plasma insulin is well documented in the Zucker fatty rat (5, 55–57). It has been shown that if this hyperinsulinemia were prevented by streptozotocin treatment, then hyperphagia was prevented but the excessive deposition of lipid continues (58, 59). This suggested that the ability to overeat in this model was closely linked to the elevated levels of insulin. The role of the CNS in the regulation of insulin secretion of the Zucker rat has recently been explored (60, 61). Increased insulin secretion in the preobese Zucker fatty rat has been shown to be an early abnormality mediated by the vagus nerve. It has been suggested that a genetically linked CNS dysfunction, possibly hypothalamic, alters the fine balance of parasympathetic and sympathetic pathways, resulting in an overactivity of the vagus nerve (62, 63).

3. Defective hypothalamic control of growth hormone release. Hypothalamic controls of growth hormone release through neuropeptides and neurotransmitters are well documented (64–67). Growth hormone levels in the obese rat were found to be lower when measured at different times of the day and at different ages (36, 68). However, when the pituitary cells from obese rats were tested *in vivo* and *in vitro,* there appeared to be no indication of a deficiency in the capacity of these cells to respond and secrete growth hormone (69). Therefore, the decrease in growth hormone status could be ascribed to an abnormal hypothalamic function. There was some indication that the hypothalamus of the Zucker fatty rat secretes more somatostatin *in vitro* than in lean rats (70) and that the obese pituitary cell response to growth hormone releasing factor is blunted (71). Based on the above information it was proposed that the mechanism by which bone and muscle development was

influenced in pair-fed Zucker fatty rats is hypothalamic in nature (Fig. 1). An abnormally high secretion of somatostatin by the hypothalamus (70) reduced growth hormone secretion by the pituitary (36) which in turn resulted in a diminished serum somatomedin activity (35). Bone and muscle growth were impaired (28) by the lack of somatomedin activity.

4. Defective reproductive function related to hormones under hypothalamic control. The reproductive cycle has been shown to be regulated by the hypothalamus, secondary to its control of pituitary function (64). Reproductive function was impaired to both male and female mature Zucker fatty rats (72). In order to maintain a colony heterozygote (*Fa/fa*) rats have had to be used for breeding. It was recently suggested that "sexual differentiation of the developing brain may be deficient in the obese Zucker" (72).

5. Defective energy balance related to tissues under the control of the hypothalamus. Studies on energy balance in the Zucker rat tend to have been focused on quantitative aspects of thermoregulation (73, 74) and the mechanisms that determine energy expenditure (16, 34, 39–41, 75–78). The sympathetic nervous system was thought to be critical for regulation of thermogenesis and has been proposed as a mechanism by which decreased energy loss as heat may cause some forms of obesity (79, 80). Some of the major afferent fibers of the sympathetic system have been

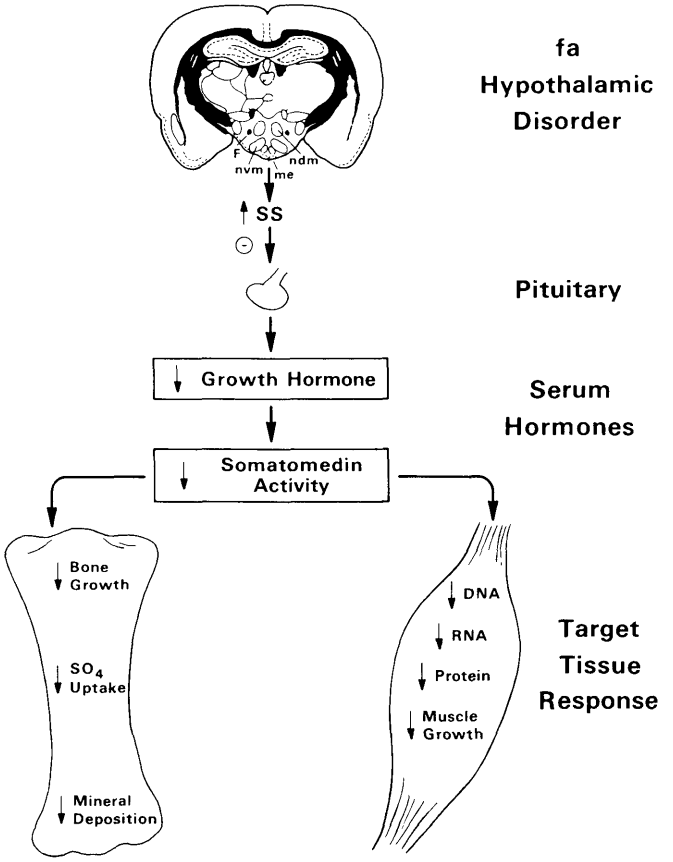

FIG. 1. Proposed *fa* gene hypothalamic mechanisms which lead to decreased bone and muscle growth. Arrows indicate change in Zucker fatty rat relative to the lean rat. F = fornix, nvm = ventromedial nucleus, me = median eminence, ndm = dorsal-medial nucleus, SS = somatostatin.

shown to originate in the ventromedial hypothalamus (81) and lesions of the ventromedial hypothalamic area have resulted in tissue specific decreases in sympathetic activity (82). Sympathetic activity has been found to be depressed in specific organs of the nonlesioned Zucker fatty rat (83–85), suggesting defective central regulation of sympathetic activity in this animal.

Insulin concentration in the CNS has been proposed as a central signal for whole-body energy balance regulation (86). The CNS content of insulin and the binding of insulin to membranes of the olfactory bulb have been shown to be severely decreased in the Zucker fatty rat (87–89), again suggesting a central defect in this obese genotype.

6. Defective metabolism of CNS neurotransmitters. It has been shown that the neurotransmitters are involved in the regulation of level of food intake, pattern of intake, and diet selection (46, 90–93). There have been some studies of levels of neurotransmitter levels in the Zucker rat (90–96). It appeared that norepinephrine, epinephrine, dopamine, and serotonin metabolism were all abnormal in the fatty rat. These changes in neurotransmitter levels could be important causal factors in the etiology of abnormal neuroendocrine secretion and energy balance. However, it was not possible to establish cause and effect relationships.

7. Defective control of neuropeptides. The understanding of the role of neuropeptides in obesity has been expanding rapidly. Some of the neuropeptides known to be involved in the regulation of feeding have been found to be altered in the Zucker fatty rat. Cholecystokinin (CKK) has been shown to be a short-term regulator of food intake (97). This peptide has been found at increased concentrations and is secreted at elevated rates in the hypothalamus of the fatty rat (98, 99), although CCK receptor binding appeared to be normal in this tissue (100). The Zucker fatty rat has also been shown to have increased serum and pituitary concentrations of β-endorphin (101, 102), an opioid known to stimulate food intake (103). Naloxone, a specific opioid antagonist, blocked opioid-induced feeding (104). The Zucker fatty rat gave an exaggerated response to naloxone, compared with lean controls (104, 105). As it has been suggested that opioids and CCK interact at the level of the hypothalamus to control food intake, it was further advanced that abnormal concentrations of these peptides could lead to hyperphagia in the Zucker rat (106).

Corticotrophin-releasing factor (CRF), a neuropeptide that influences the pituitary–adrenal axis, has also been implicated in the development of the Zucker fatty rat. There has been a substantial amount of evidence that abnormal functioning of the adrenal gland was important in the development of obesity in the fatty rat (107), there was also some indirect evidence that secretion of CRF was elevated in these animals. While serum levels of corticosterone appeared to be normal, based on a single blood sample, an abnormal diurnal pattern of serum corticosterone concentration has been demonstrated (68). An excessive urinary loss of corticosterone and a dampened pituitary response to CRF have been reported (108) and adrenalectomy of the fatty rat reduced food intake, fat appetite and inhibited weight gain (107, 109, 110).

Several lines of evidence have been discussed that suggest that the initial common pathway for induction of excessive lipid deposition in the Zucker fatty rat involves a hypothalamic disturbance. However, elimination of specific regions of the brain, involved in the regulation of energy balance, have failed to reverse the obesity. Both selective lateral hypothalamic lesions (111) and serotonin depleting midbrain lesions (112) have failed to mitigate the obesity. If the genetic defect is in the synthesis of a neuropeptide, or in the synthesis of a key enzyme involved in CNS metabolism, then it seems that a different approach is required to identify the primary cause of obesity in the Zucker fatty rat.

Summary. Several lines of evidence are cited in support of the hypothesis that the genetic defect in the Zucker fatty rat occurs in the central nervous system. A number of abnormalities in hypothalamic neurotransmitters and neuropeptides have been identified and have the potential to influence the level of food intake, the endocrine status and finally the capacity for lipid storage in the fatty rat. Large increases in liver and adipose lipogenic capacity can be attributed to elevated levels of food

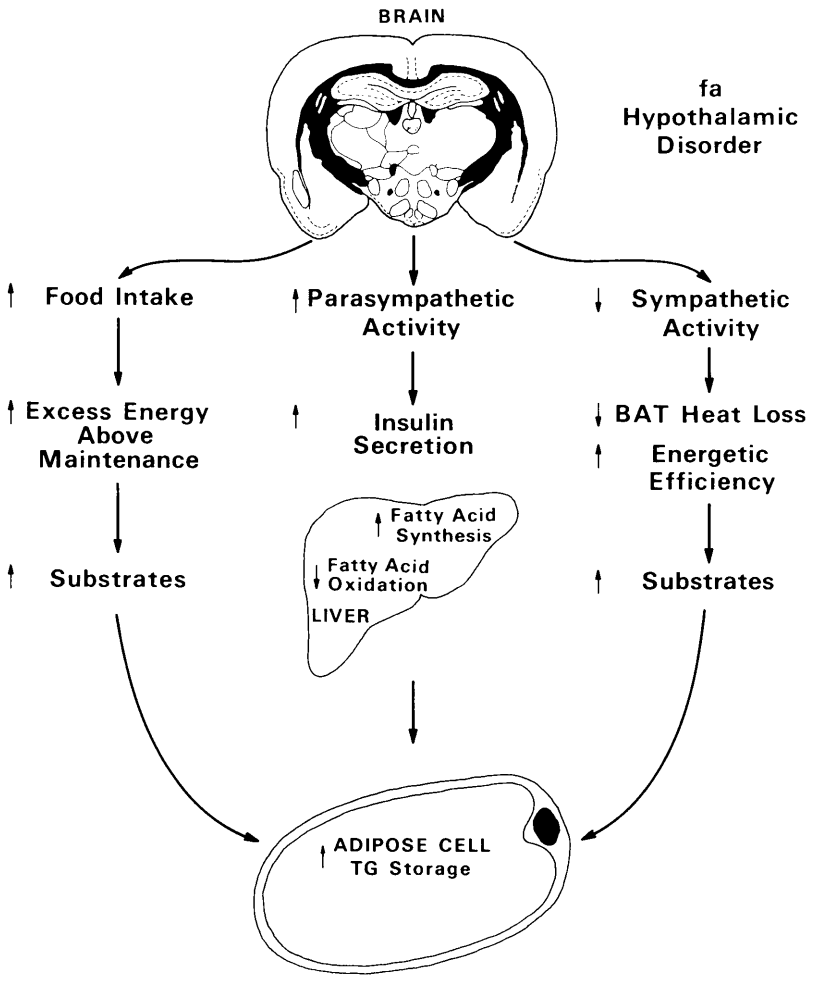

FIG. 2. Proposed *fa* gene hypothalamic mechanisms which combine to influence the partitioning of nutrients and the efficiency of net energy utilization. The arrows indicate change in the Zucker fatty rat relative to the lean rat. Increased food intake above maintenance requirements results in more substrates available for fatty acid synthesis and lipid deposition. Increased parasympathetic activity results in an increased insulin release which favors lipid synthesis and decreases lipid oxidation. Decreased sympathetic activity results in decreased BAT activity and increased energetic efficiency and substrates available for adipose cell synthesis of triglyceride.

intake and to hyperinsulinemia combined with an apparent decrease in sympathetic activity. Decreased efficiency of protein utilization for muscle and bone growth may be linked to low circulatory levels of growth hormone and somatomedin combined with an elevated glucocorticoid status. These large shifts in neuroendocrine status (Fig. 2) result in an environment that favors the partitioning of exogenous energy toward lipid deposition and obesity.

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