The Zucker Fatty Rat as a Genetic Model of Obesity and Hypertension

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The association of hypertension with obesity has long been recognized; however, because of the lack of suitable animal models of obesity and hypertension, the pathogenesis of the high blood pressure associated with obesity remains poorly understood. We hypothesized that the Zucker fatty rat, a widely studied model of obesity and insulin resistance, might also be characterized by hypertension. Mean arterial pressure directly measured in the unanesthetized, unrestrained obese (fatty) Zucker rat was significantly greater than in two strains of nonobese control rats, the lean Zucker rat and the Lewis rat. The greater blood pressure in the obese rats was not dependent on hyperphagia or increased body weight per se since moderate caloric restriction, achieved by pair-feeding with lean rats, decreased weight gain but did not attenuate hypertension. Pair-fed obese rats retained less sodium than lean control rats, suggesting that greater blood pressure in the obese rats is not a consequence of increased renal retention of sodium. A unique feature of the Zucker strain is that the increased blood pressure appears to be specifically associated with the obese genotype. The findings suggest that the obese Zucker rat might provide a useful experimental model of obesity and hypertension. (Hypertension 1989;13:896-901)

The association of clinical hypertension (high blood pressure) with obesity is well recognized. In a recent survey in which body weight and blood pressure were measured in 1 million Americans, Stamler et al1 found that hypertension was twice as prevalent in younger overweight subjects and 50% more prevalent in older obese individuals than in normal-weight control subjects. However, despite the well-established association between obesity and hypertension, the pathophysiological relation between obesity and hypertension remains poorly understood. Lack of information regarding the pathogenesis of the high blood pressure associated with obesity has been attributed, in part, to the lack of suitable animal models of obesity and hypertension.2

In the dog, Rocchini and colleagues2 have found that sustained administration of excess calories can induce obesity and hypertension; however, in the rat, overfeeding alone does not readily increase blood pressure.3 A few strains of spontaneously obese, hypertensive rats have been described, but frankly increased blood pressure also occurs in the nonobese littermates used as control rats.4,5 Thus, these strains are of limited use in studying the pathogenesis of hypertension associated with obesity because the increased blood pressure is largely independent of the obese genotype.

Insulin resistance, a common feature of obesity, has been reported in nonobese patients with high blood pressure, and it has been proposed that insulin resistance is an important pathogenetic determinant of hypertension.6 Accordingly, we hypothesized that the Zucker fatty rat,7 a well-established model of obesity and insulin resistance,8 might also be characterized by hypertension. Although it has been stated that the obese (fatty) Zucker rat is not hypertensive,3,4 direct measurements of mean arterial pressure in unanesthetized Zucker rats have never been reported. To test the hypothesis that the Zucker rat provides a genetic model of obesity and hypertension, we directly measured mean arterial pressure in unanesthetized, unrestrained obese Zucker rats; lean Zucker and lean Lewis rats were used as normotensive controls. Our findings demonstrate that the blood pressure of the obese Zucker rat is greater than that of the two lean control rats.
and that the hypertension is not just a consequence of hyperphagia and increased caloric intake. Furthermore, in the obese rat, blood pressure is significantly greater than that in the lean control rats, despite lesser retention of sodium.

Materials and Methods

Five-week-old female obese (fa/fa) and female lean (Fa/Fa or Fa/fa) Zucker rats were obtained from Charles River Laboratories (Wilmington, Massachusetts) and individually housed in metabolic cages. The animals were pair-fed a standard purified rat diet (American Institute of Nutrition diet AIN-76A, Teklad, Madison, Wisconsin) consisting of, by weight, 65% carbohydrate, 18% protein, 5% fat, 5% fiber, and 0.1% Na+ with the remainder consisting of water, mineral mix, and vitamins. The carbohydrate supplied 69% of total calories; protein, 19%; and fat, 12%. A pair-feeding protocol was followed in which the daily amount of food given to each obese rat was determined by the daily amount of food ingested by a paired, lean control. Tap water was provided ad libitum. All studies were conducted in accordance with the guidelines of the Committee on Animal Research of the University of California, San Francisco. Daily 24-hour urine samples were collected throughout the study and preserved with 0.5 cc 5N HCl. In each rat, the external balance of sodium was determined by subtracting the urinary excretion of sodium from the dietary intake of sodium. The urine concentration of sodium was measured by flame photometry.

After 4 weeks, mean arterial pressures were measured in the unanesthetized, unrestrained state through indwelling femoral artery catheters. Each rat was briefly anesthetized with methoxyflurane, and a catheter (PE-50) was implanted in the femoral artery with the distal end tunneled subcutaneously to an exit in the nape of the neck. The catheter was filled with a heparinized solution of 5% dextrose and plugged with a stainless steel obturator. After surgery, each rat was returned to its cage to recover from anesthesia; blood pressures were measured 4-6 hours after stopping the anesthetic agent at a time when the animals were fully alert and roaming freely within their cages.

To measure blood pressure, the femoral catheter was connected via an extension catheter (PE-50) to a low-volume pressure transducer (model P50, Gould Inc., Cleveland, Ohio). The measurement of blood pressure was begun 30-60 minutes after connecting the catheter to the transducer. The output of the transducer was sent to a Gould transducer preamplifier, and the mean arterial pressure signal was passed to an analog-digital (A/D) converter (DASH-8, Metabyte Co., Taunton, Massachusetts) installed in an IBM AT microcomputer. Data acquisition software (Labtech Notebook, Laboratory Technologies Co., Wilmington, Massachusetts) was employed to sample the blood pressure signal every 15 seconds over a period of 2 hours. The average of these 480 measurements obtained over 2 hours was then calculated to yield each rat’s mean arterial pressure. In each rat, the coefficient of variation of the 480 blood pressure measurements was determined by dividing the standard deviation of the measurements by the mean of the measurements. Statistical analysis was performed with Student’s t test and the Bonferroni correction for multiple comparisons.

Results

After the 4-week metabolic study, mean arterial pressure measured in the obese rats was significantly greater than that in the lean Zucker control rats (Figure 1). Blood pressure variability in the obese rats appeared similar to that in the lean rats. In the obese rats, the mean coefficient of variation of the blood pressure measurements, 5±0.6% (mean±SEM), was not significantly different from that in the lean rats, 4±0.7%. The mean weekly food intake of the obese rats was not different from that of the lean rats (Figure 2). However, the mean body weight of the obese rats was significantly greater than that of the lean Zucker controls (Figure 2). The observation of greater body weight in the obese rats than in the lean Zucker control rats, despite pair-feeding, accords with previous studies in pair-fed obese Zucker rats in which greater increases in weight and in total body fat have been reported compared with lean Zucker rats. Although blood pressure and body weight were significantly increased in the obese rats, the obese rats retained less sodium than the lean rats (Figure 3). In the obese rats, the decreased retention of sodium may have been a consequence of starvation natriuresis since the caloric restriction associated with pair-feeding may constitute a state of relative starvation for these animals.
To confirm that the greater blood pressure observed in the obese Zucker rat was not simply a consequence of employing a control strain with uniquely low blood pressure, another study was performed in which blood pressure of the obese Zucker rat was compared with that of a different control rat, the commonly used inbred Lewis rat. Nine weanling female obese Zucker rats and nine weanling female Lewis rats were obtained from Charles River Laboratories and were entered into a metabolic balance study in which the animals were pair-fed as previously described. To determine if the pair-feeding protocol attenuated hypertension in the obese Zucker rats, blood pressures were also measured in nine additional female obese Zucker rats that were housed in metabolic cages and fed ad libitum.

After 6 weeks, mean arterial pressure of the obese rats was significantly greater than that of the control Lewis rats (Figure 4), despite pair-feeding (Figure 5). The mean body weight of the pair-fed obese rats tended to be greater than that of the Lewis rats, but the difference was not statistically significant (Figure 5). The cumulative amount of sodium retained by the pair-fed obese rats was significantly less than that retained by the control Lewis rats (Figure 6). The mean body weight of the pair-fed obese rats was less than that of the obese rats fed ad libitum (Figure 5); however, mean arterial pressures were not different between the two groups (Figure 4). Thus, in the obese rats, the
pair-feeding protocol decreased weight gain but did not decrease blood pressure.

Discussion

The current findings demonstrate that in unanesthetized, unrestrained, obese female Zucker rats, mean arterial pressure is greater than that in lean Zucker rats or Lewis rats. Thus, the apparently increased blood pressure in the Zucker fatty rat is not a consequence of using a specific control strain with uniquely low blood pressure. Because the obesity and increased blood pressure occur spontaneously, the Zucker fatty rat from Charles River Laboratories appears to provide a genetic model of obesity and hypertension.

In a study of the effects of genetic obesity on renal function, Kasiske et al. found that systolic blood pressure, measured with the indirect tail-cuff technique in the unanesthetized state, was significantly greater in obese Zucker rats fed ad libitum than in lean Zucker rats. However, these investigators could not confirm the presence of hypertension when mean arterial pressure was directly measured in the anesthetized state. Bass and Ritter claimed that mean arterial pressure in unanesthetized, unrestrained obese Zucker rats was not different from that of lean Zucker rats; however, these investigators did not publish any blood pressure data or information on the number of rats studied. In a small study of anesthetized obese (n=5) and lean (n=6) Zucker rats, Levin et al. found no difference in blood pressure between the two strains. In their study, however, mean arterial pressures were extremely low, approximately 80 mm Hg. In contrast, in another study in anesthetized Zucker rats, Wickler et al. found increased arterial blood pressure in the obese strain. The well-known problems associated with indirect tail-cuff measurements of blood pressure, as well as with measurements of blood pressure in anesthetized animals, limit the interpretation of these studies.

In the current study, we measured blood pressure 4-6 hours after surgical implantation of the femoral artery catheters, and it is possible that the greater blood pressure in the obese rats was a consequence of greater reaction to the surgical stress. However, we observed no evidence of postoperative pain or suffering (e.g., vocalization or abnormal locomotion) in either the lean or obese rats. The duration of surgery and of recovery from anesthesia was similar in both groups. The overall appearance and behavior of the obese rats was also similar to that of the lean rats. Finally, our results are in agreement with studies in unanesthetized obese Zucker rats in which increased blood pressure has been demonstrated with the noninvasive tail-cuff method.
In 1973, Koletsky\textsuperscript{18} described the spontaneous occurrence of obesity in a hypertensive rat (the Koletsky rat) that had descended from the mating of a spontaneously hypertensive rat (SHR) and a normotensive Sprague-Dawley rat. Breeding data from crosses of the Zucker rat and the Koletsky rat suggest that alleles at the same locus may be responsible for the obesity in these strains.\textsuperscript{19} However, in Koletsky rats,\textsuperscript{4,18} like in other strains of obese SHRs,\textsuperscript{5} hypertension also predictably occurs in the nonobese littermates used as control rats. In a recently established congenic strain of genetically obese rats (SHR/N-corpulent), blood pressure in the obese animals was found to be lower than that in the lean congenic controls.\textsuperscript{20} Thus, in all of these genetically obese strains, increased blood pressure is not specifically associated with the obese genotype. Such strains would not seem to be suitable for investigating the pathogenetic relation between obesity and hypertension.

A unique feature of the Zucker strain is that the increased blood pressure appears to be specifically associated with the obese genotype (fa/fa). Because the phenotypically lean Zucker rats used in this study were of unknown genotype (some being Fa/fa, others Fa/Fa), we could not determine whether a heterozygote effect on blood pressure was operative. In Zucker rats, a heterozygote effect has been demonstrated with respect to body weight, total body fat, and pancreatic insulin release.\textsuperscript{21} It is conceivable that the presence of a single fa allele is associated with increased blood pressure and that in heterozygous lean rats, blood pressure is slightly greater than in homozygous lean rats.

It is widely believed that certain physiological or metabolic disturbances associated with obesity such as insulin resistance and hyperinsulinemia, are pathogenetic determinants of increased blood pressure. However, it is also possible that the physiological and metabolic side effects of obesity do not primarily account for the hypertension associated with obesity. In the Zucker rat, it remains to be determined whether: 1) side effects of genetic obesity cause high blood pressure, 2) the locus determining obesity codes for a protein that causes both the obesity and the high blood pressure, or 3) the locus determining obesity is closely linked to loci determining high blood pressure.

In the obese Zucker rats, we found that moderate caloric restriction, achieved by pair-feeding the obese rats with lean rats, reduced weight gain but did not attenuate hypertension. Although this might suggest that the hypertension is independent of obesity, it should be noted that moderate caloric restriction may not fully correct all of the physiological and metabolic disturbances associated with obesity. For example, in the obese Zucker rat, restriction of food intake to the amount ingested by the lean Zucker control rat does not fully correct hyperinsulinemia.\textsuperscript{11} Furthermore, the antihypertensive effect of caloric restriction may be more a function of the severity of caloric restriction and rapidity of weight loss than absolute reduction in body weight.\textsuperscript{22} Thus, in the obese Zucker rat, just as in some humans with obesity and hypertension, moderate caloric restriction may not be sufficient to attenuate hypertension; severe caloric restriction, or moderate caloric restriction combined with sodium restriction, may be required to decrease blood pressure.\textsuperscript{23,24}

In normotensive rats, increased intake of simple carbohydrates per se can increase blood pressure.\textsuperscript{25,26} In the obese Zucker rats, the occurrence of increased blood pressure despite pair-feeding suggests that the hypertension is not just a consequence of hyperphagia and increased caloric intake. However, it is also conceivable that in the food-restricted obese rats, the persistence of hypertension reflects a stress response to the pair-feeding protocol.

The current study was designed to determine whether the Zucker rat might provide a model of obesity and hypertension and did not attempt to investigate the multitude of hemodynamic, endocrine, and neural factors that could potentially mediate the hypertension associated with obesity.\textsuperscript{27} However, given that insulin resistance and hyperinsulinemia are major features of the obese Zucker rat,\textsuperscript{4} the recent proposal that insulin resistance and hyperinsulinemia may be important pathogenetic determinants of hypertension merits specific consideration.\textsuperscript{4} Insulin has been shown to increase renal tubular reabsorption of sodium, and it has been proposed that insulin-induced sodium retention is a pathogenetic determinant of obesity-related hypertension.\textsuperscript{28} In the current study, however, the pair-fed obese Zucker rats retained less sodium than either the lean Zucker control rats or the Lewis rats. Thus, increased blood pressure in the obese Zucker rat may not simply be a consequence of an insulin-induced increase in renal retention of sodium. Although an insulin-induced increase in sodium retention may not account for the hypertension in this model, hyperinsulinemia might contribute to increased blood pressure through a variety of other mechanisms.\textsuperscript{27,29}

In the current study, the mean serum creatinine level of 9–10-week-old obese Zucker rats, 0.6±0.1 mg/dl, was not significantly different from that in age-matched lean Zucker control rats, 0.5±0.1 mg/dl, which suggests that decreased glomerular filtration rate does not account for the hypertension in the obese rat. In a study of the effects of genetic obesity on renal function in the Zucker strain, Kasiske et al.\textsuperscript{12} found that glomerular filtration rate, as judged by inulin clearance, was also normal in 12–14-week-old obese rats. These investigators noted that urinary excretion of albumin was mildly increased in 12-week-old obese Zucker rats, which may have been due to the transmission of increased systemic arterial pressure to the glomerular capillary bed.\textsuperscript{12}
Whatever the relation between obesity and hypertension, the current study, in demonstrating that blood pressure in the obese Zucker rat is greater than that in the lean Zucker control rat, has identified a rat model that might provide unique opportunities to investigate the pathogenesis of hypertension associated with an obese genotype. Because the obese Zucker rat exhibits insulin resistance and develops an intense fibrocellular proliferative response to the disruption of aortic endothelium, this strain might also be useful for studying the interaction of hypertension and disordered carbohydrate metabolism in the pathogenesis of vascular disease and accelerated atherosclerosis.

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